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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

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PREVALENCE OF BREAST CANCER IN HUMAN POPULATIONS

1. GEOGRAPHICAL VARIATIONS IN CANCER INCIDENCE IN TWO URBAN POPULATIONS IN INDIA.

Jussawalla DJ, Yeole BB, Natekar MV, Rajagopalan TR
Bombay Cancer Registry, Indian Cancer Society, Parel, Bombay 400 012, India
Indian J Cancer; 18(2):91-98 1981

The variation in cancer incidence between the populations of Greater Bombay and Poona City was investigated by age, sex, and site. Both age adjusted and truncated rates are reported and a simplified statistical method was used for testing the variations. Between 1972 and 1974, there were 12,969 new cancer cases in Bombay and 2,670 new cases in Poona City. The sex distribution showed many more males than females in Bombay (7,428 vs 5,541) than in Poona City (1,346 vs 1,324). In both areas cancer incidence increased sharply with age. In Bombay, more cancers of the tongue, pharynx, esophagus, and lung were seen, while in Poona City, more cancers of the stomach, buccal mucosa, rectum, and penis in males, and stomach, breast, uterus and cervix in females were seen. These differences are attributed to differences in the environmental, geographical and demographic status of these two cities. (10 Refs)

2. THE CENTRAL CANCER REGISTRY OF THE HEALTH COMMISSION OF NEW SOUTH WALES.

McEwin R, Ford J, Goulston K
Health Commission of New South Wales, New South Wales, Australia
Cancer Forum; 5(1):19-24 1981

A review of the New South Wales (NSW) Cancer Registry, a unit of the Health Commission of New South Wales, is presented. The registry has been in operation since 1972 with the following aims: to delineate the nature and extent of cancer in NSW, to provide information which can be used in the control and prevention of cancer, to explore and determine the etiological aspects of cancer, and to describe the natural history of all types of cancer. The 1976 data show that in NSW, the leading sites of cancer in males were lung and colon and rectum; in females, they were breast and colon/rectum. The commonest cancer was skin cancer, but data are not collected for squamous and basal cell carcinoma of the skin. The data in the registry are presented as cross-tabulations for new cases and deaths, by age and sex, related to cancer sites, subsites, and cell types: for the State, Health Regions, Local Government areas, and for various ethnic groups. Applications of the data in the registry are discussed. (2 Refs)

3. EPIDEMIOLOGY OF CANCER.

Pawlega J
Pracownia Epidemiologii, Oddzial Instytutu Onkologii w Krakowie, ul. Garncarska 11, 31-115 Krakow, Poland
Przegl Lek; 38(5):447-451 1981

Cancer epidemiological data are presented for Krakow (urban area) and a nearby rural area for the period from 1965 on the basis of Cancer Registry data. The overall standardized cancer morbidity (per 100,000 population) in men in Krakow was 285 (70.9 for lung cancer, 35.1 for gastric cancer, 22.9 for skin cancer, 12.3 for pancreatic cancer, and 11.0% for urinary bladder cancer). The overall cancer mortality for men in the rural area was 177.1 (38.9 for lung cancer, 33.1 for gastric cancer, 9.6 for skin cancer, 8.3 for prostate cancer, and 8.0 for urinary bladder cancer). The cancer morbidity for women in Krakow was 201.1 (37.7 for breast cancer, 22.0 for cancer of the uterine cervix, 14.8 for gastric cancer, 14.9 for skin cancer, and 12.7 for lung cancer). The corresponding figures for the rural women were 122.1 (overall morbidity); 17.2 for gastric cancer, 17.8 for breast cancer. The percentage of cases diagnosed histologically was higher among the urban than among the rural patients, and the percentage of the patients not receiving antitumor therapy was higher among the latter. The relative 5-yr survival rates in men were higher among the urban patients than among the rural ones for all major localizations (lips, stomach, rectum, larynx, lungs, prostate, and bladder) except skin cancer, and the relative 5-yr survival of the urban women was higher for all major localizations (cancer of the stomach, skin, breasts, uterine cervix, endometrium, ovaries, and leukemia). (16 Refs) (In POL)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

4. BREAST CANCER INCIDENCE IN WOMEN WITH A HISTORY OF PROGESTERONE DEFICIENCY.

Cowan LD, Gordis L, Tonascia JA, Seegar Jones G
Lipid Res. Clinic, Population Studies, Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Am J Epidemiol; 114(2):209-217 1981

In order to investigate the nature of the association of involuntarily delayed first birth and risk of breast cancer, 1,083 white women who had been evaluated and treated for infertility from 1945-1965 were followed prospectively through April 1978 to ascertain their breast cancer incidence. These women were categorized as to the cause of infertility into two groups, those with endogenous progesterone deficiency (PD) and those with nonhormonal causes (NH). Women in the PD group had 5.4x the risk of premenopausal breast cancer compared to women in the NH group. This excess risk could not be explained by differences between the two groups in ages at menarche or menopause, history of oral contraceptive use, history of benign breast disease or age at first birth. Women in the PD group also experienced a 10-fold increase in deaths from all malignant neoplasms compared to the NH group. The incidence of postmenopausal breast cancer did not differ significantly between the two groups. (Author abstract) (23 Refs)

5. ELEVATED URINE ESTROGEN AND PREGNANEDIOL LEVELS IN DAUGHTERS OF BREAST CANCER PATIENTS.

Trichopoulos D, Brown JB, Garas J, Papaioannou A, MacMahon B
(c/o MacMahon) Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115
JNCI; 67(3):603-606 1981

Urine levels of three major estrogens and of pregnanediol were measured for 76 nulliparous daughters of breast cancer patients and for 115 control women of similar age and parity. Concentrations of estrone and estradiol tended to be higher in the daughters of breast cancer patients than in the controls; total estrogens were elevated in both phases of the menstrual cycle and significantly so in the luteal phase. There was little difference between the daughters and the controls in estriol ratios-the ratios of the concentration of estriol to the sum of the concentrations of estrone and estradiol. Pregnanediol levels were higher in the daughters than in the controls. (Author abstract) (12 Refs)

6. ANALYSIS OF A MAMMOGRAPHY ARCHIVE. RETROSPECTIVE STUDY OF PATIENTS EXAMINED IN THE TEN YEAR PERIOD 1967-1976.

De Nigris E, Romagnoli R, Amici F, Colombi A
Cattedra di Radiologia, Univ. degli Studi di Ancona, Ancona, Italy
Arch Sci Med (Torino); 138(3):423-430 1981

The statistical analysis and identification of some elements in a mammography archive of mammary cancer patients are presented. When compared with healthy women, or those with benign neoplasia, or dysplasia, or those suspected of malignity, or inflammation, the breast cancer patients distinguish themselves by an increase in av age, late menopause, early menarche, increase in the interval between the menarche and the first full term pregnancy, family history of malignancies of all types and exclusively of breast localization, increase in surgery of uterus and its appendages, increase in parity, and increase in breast feeding time. (14 Refs) (In ITA)

7. THE EPIDEMIOLOGY AND PATHOGENESIS OF THE MAMMARY CANCER.

Pimentel E
Catedra de Fisiopatologia, Universidad Central de Venezuela, Caracas, Venezuela
Rev Fac Med Univ Cent Venez; 1(1):27-47 1981

The mammary cancer is five to six times more frequent in the northern countries of Europe and in North America, than in Asia and Africa. The southern European countries and South America are in between. This is a general rule with notable exceptions. In 1978 in Venezuela the total cancer mortality was 13.5%. The mammary cancer was 9.6% of the total women cancer mortality and it was in the fourth place. In the United States the mammary cancer was in the first place with 13.6% of the total women cancer mortality. The pathogenic factors are endogenous (genetic, immunologic, hormonal, reproductive, neural) or exogenous (diet, ionizing irradiation, chemical carcinogens, oncologic viruses). The relative importance of each factor is very variable from one species to another and there are notable differences between various stocks of the same species. The pathogenic factors of human mammary cancer are not well known. The genetic factors seem to be important in the minority of cases. The immunologic and hormonal factors probably are not involved in the transformation of the normal cells, but they influence the growth of neoplastic cells. There are no carcinogenic substances known which play a role in the origin of the human mamma ry cancer. A minority of cases are related to ionizing irradiation. The possible role of virus is not yet elucidated. (63 Refs) (In SPA)

8. ACANTHOSIS NIGRICANS, FLORID CUTANEOUS PAPILLOMATOSIS AND THE SIGN OF LESER-TRELAT.

Schwartz RA
4150 Clement St., Dept. Dermatology, San Francisco, CA, 94121
Cutis; 28(3):319-322,326-327,330-331,334 1981

Association between acanthosis nigricans (AN), florid cutaneous papillomatosis, and the sign of Leser-Trelat, and the relation of the three entities with underlying malignancy are reviewed. Four types of AN are recognized: benign, pseudo, AN as part of a syndrome, and AN associated with malignancy. Among syndromes associated with AN are insulin resistance and AN (types A and B), polycystic ovary disease, pituitary tumor syndromes, and Bloom's syndrome. Cancer associated with AN ('malignant AN') is characterized by rapid onset and spread. Cancer sites include stomach, esophagus, breast, prostate and bronchus. The cancer is usually discovered simultaneously with or after onset of AN. Upon discovery of malignant AN a vigorous effort must be made to identify the responsible tumor. AN may regress with excision and may recur with metastatic disease. In one review of 26 cases of cancer with sign of Leser-Trelat (abrupt appearance and rapid increase in size of many seborrheic keratoses), 20 involved adenocarcinomas (including colon, stomach, pancreas, breast, ovary, etc) and 6 involved mycosis fungoides, lymphoma, squamous cell lung carcinoma and leukemia. Etiology of malignant AN, florid cutaneous papillomatosis, and the sign of Leser-Trelat is unknown. (60 Refs)

9. BREAST CANCER AND TRH - RESPONSE.

Kohler AH, Kuhnel W, Kilz F

Bezirkskrankenhaus Cottbus, Radiologische Klinik, Thiemstrasse 111, 7500 Cottbus, E. Germany

Arch Geschwulstforsch; 51(3):273-278 1981

The hypothesis that hypothyroidism may be related to breast cancer was tested. Thiry-seven patients with histologically-confirmed breast cancer were compared with 30 healthy controls. All patients were postmenopausal, with a median age of 62.3 yr. They were examined 10 days after radical mastectomy. Assays measured serum creatinine, triiodothyronine binding capacity, and thyroid stimulating hormone (TSH). The effect of thyrotropin releasing hormone (TRH) on TSH levels was measured. After TRH stimulation (200 ug iv) the mean TSH level was 10.82 uIU/ml in the patient group and 12.70 uIU/ml among controls. The difference was not statistically significant. The results did not support a relationship between hypothyroidism and breast cancer. (35 Refs)

POSSIBLE IATROGENIC FACTORS IN HUMAN BREAST CARCINOGENESIS

10. BREAST CANCER, PREGNANCY, AND THE PILL.

Drife JO

Univ. Dept. Obstetrics and Gynaecology, Bristol Maternity Hosp., Bristol BS2 8EG, England

Br Med J; 283(6294):778-779 1981

Roles of parity and oral contraceptive use in the etiology of breast cancer are discussed. Clear histological and physiological changes are observed in the breast following pregnancy. A decrease in number of clear cells and an altered response to hormones is seen after a single pregnancy. Cyclic DNA and IgA synthesis are found only in parous women. Plasma concentrations of estrogen and progesterone are similar in both parous and nulliparous women, but pregnancy permanently alters the hormonal responsiveness of breast epithelium. The carcinogenic effect of estrogen unopposed by progesterone on the breast is hypothesized. Prior to pregnancy a woman has an inadequate number of endogenous progesterone receptors so that even with a combined estrogen-progesterone contraceptive pill, breast tissue may in effect experience 'unopposed' estrogen. Nulliparity and delayed first pregnancy may be important risk factors for subsequent breast cancer. Future study should focus not on hormonal profile but on effects of hormones on the breast itself. (24 Refs)

11. THE INFLUENCE OF GESTAGEN-ORIENTED ORAL CONTRACEPTIVES ON THE MILK DUCT EPITHELIUM - CYTOLOGICAL FINDINGS IN MAMMARY SECRETIONS.

Wunderlich M

Gynakologisch-Geburtshilfliche Klinik, Kreiskrankenhauses Altenburg, 7400 Altenburg, E. Germany

Dtsch Gesundheitswes; 36(27):1139-1141 1981

The general influence of oral contraceptives on breast parenchyma and their ability to stimulate pathophysiological secretion have been repeatedly described; yet there are no investigations concerning specific preparations. On the basis of a number of our own patients we showed that especially after long-term ingestion of Nonovlon - a gestagen-oriented contraceptive - a conspicuous number of mild and moderate types of dysplasia of the cells of the mammary secretion could be found in cytological examinations. Without drawing any binding conclusions, these findings should stimulate further intensive research investigations in order to avoid probable dangerous side-effects after long-term administration of oral contraceptives. (Author abstract) (16 Refs) (In GER)

12. INFLUENCE OF CONJUGATED OESTROGENS ON CIRCULATING OESTRADIOL, OESTRONE, LH, FSH AND PROLACTIN LEVELS IN POSTMENOPAUSAL WOMEN.

Luisi M, Franchi F, Argenio GF, Barletta D, Romano MR, Bernini GP, Gasperi M, Sgrilli R

Postgraduate Sch. Endocrinology and Endocrine Unit C.N.R., Pisa Univ. Sch. Medicine, 56100 Pisa, Italy

Int J Tissue React; 3(2):77-81 1981

The effect of a conjugated estrogen (Equormon-ION; obtained from pregnant mares' urine; 1.5 mg/day for 20 consecutive days po) on plasma 17-beta-estradiol (E2), estrone (E1), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin (PRL) levels was studied in six 60-68-yr-old menopausal women. The time elapsed from surgical or spontaneous menopause was 6-12 yr. The plasma E1 level increased significantly from 28 picog/ml before treatment to 108 picog/ml after 20 days of treatment (p less than 0.001). Five days after the last dose of the conjugated estrogen, the mean plasma levels of both steroids were similar to the control values. The mean plasma levels of LH and FSH decreased progressively and significantly from 114 and 105 milli units (mU)/ml, respectively, before treatment to 43 and 36 mU/ml, respectively (p less than 0.001). Both the LH and FSH levels were significantly higher 5 days after the estrogen treatment than at its end (p less than 0.001). The conjugated estrogen treatment has no significant effect on the pattern of pituitary PRL secretion. The preliminary results seem to indicate that the possible effects of elevated plasma prolactin levels, usually observed during long-term estrogen treatment in menopausal women, on the development and growth of breast cancer, could be avoided. (16 Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

13. CARCINOGENICITY OF BENZIDINE, N,N'-DIACETYLBENZIDINE, AND N-HYDROXY-N,N'-DIACETYLBENZIDINE FOR FEMALE CD RATS.

Morton KC, Wang CY, Garner CD, Shirai T

Dept. Chemical Carcinogenesis, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201

Carcinogenesis; 2(8):747-752 1981

Female CD rats were given twice-weekly ip injections for 4 wk, beginning at 30 days of age. Each of nine groups was given one of the following doses: 20 or 70 umol benzene (BZ)/mg body wt/ injection; 7, 22, or 70 umol N,N'-diacetylbenzene (DAB)/kg; or 7, 22, or 70 umol N-hydroxy-N,N'-diacetylbenzene (HDAB)/kg. A toxicity test showed HDAB to be the most toxic of the three compounds, producing chemical peritonitis and death in all animals given the higher dosage. Additional groups were given 10 or 30 umol of one of the three compounds. Toxicity was low in all groups. BZ and HDAB showed about equal carcinogenicity. The higher dose of BZ produced mammary tumors, classified as fibroadenomas or adenocarcinomas, in 41% of the animals tested. The same dose produced Zymbal's gland tumors, classified as adenomas or carcinomas, in 24% of the animals tested. DAB and HDAB appeared to be as potent as BZ in inducing tumors. HDAB produced local reactions in the peritoneum, indicating that it may be an activated carcinogenic form of BZ. (33 Refs)

14. CARCINOGENIC POTENTIAL OF ROTENONE: SUBCHRONIC ORAL AND PERITONEAL ADMINISTRATION TO RATS AND CHRONIC DIETARY ADMINISTRATION TO SYRIAN GOLDEN HAMSTERS.

Freudenthal RI, Leber AP, Thake DC, Baron RL

Stauffer Chemical Co., Westport, CT

Carcinogenic Potential of Rotenone: Subchronic Oral and Peritoneal Administration to Rats and Chronic Dietary Administration to Syrian Golden Hamsters. Available from National Technical Information Service, Springfield, VA as PB81-190936, 47 pp., 1981.

Three long-term studies were performed to evaluate the carcinogenic potential of the pesticide rotenone in hamsters and rats. Rotenone was administered po to Wistar rats and by ip injection to Sprague-Dawley rats, which were maintained and observed for 14 and 18 mo, respectively. Syrian golden hamsters were maintained for 18 mo on diets containing rotenone in concentrations up to 1,000 ppm. Following these studies the animals were subjected to extensive necropsy. No evidence of an increased incidence of mammary or any other type of neoplasm was noted in the two rat studies. At all dosage levels in the hamster dietary study, no gross or histopathological evidence was obtained to suggest that rotenone induced the formation of mammary tumors. Three adrenal cortical carcinomas were observed in 65 hamsters from the highest dosage group; while suspicious, it is questionable that this occurrence was related to rotenone treatment. There were no other indications of neoplastic events. In ancillary studies there was preliminary evidence that rotenone at levels of 500 ppm in the maternal diet was embryo-toxic and resulted in cannibalism of the young by the maternal animals. A level of 1,000 ppm led to sterility in one or both sexes. Hamsters fed rotenone displayed reduced feed consumption and diminished wt gains during the first few mo of administration. (Author abstract)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

15. EFFECTS OF HEXESTROL, MEDROXYPROGESTERONE ACETATE AND CHLORMADINONE ACETATE ON 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED RAT MAMMARY CANCER IN RELATION TO ESTROGEN RECEPTOR.

Tominaga T, Kitamura M, Saito T, Itoh I
Dept. Surgery, Tokyo Metropolitan Komagome Hosp., Honkomagome 3-18-22, Bunkyo-ku, Tokyo 113, Japan
Gan; 72(4):604-609 1981

The effects of hexestrol (HXS), medroxyprogesterone acetate (MAP) and chlormadinone acetate (CMA) on 7,12-dimethylbenz[a]anthracene-induced mammary cancer in rats were evaluated. As a result of successive im injections of HXS at dosages of 2 or 10 mg/kg or MAP at dosages of 24 or 120 mg/kg, tumors were markedly reduced in size in all groups on day 7-day 14. These effects were the same regardless of the presence or absence of cytoplasmic estrogen receptors (ER) in tumors as determined by the dextran-coated charcoal method. Although such an effect was also seen with CMA, it was much less marked than the effects seen with HXS and MAP. The body wt of HXS-administered groups decreased considerably, whereas those of MAP-administered groups increased. These results may suggest that there is another endocrinological tumor-suppressing mechanism besides the mechanism involving the estrogen-ER system in large-dose administration of HXS and MAP. (Author abstract) (13 Refs)

16. EFFECT OF OVARIECTOMY ON SERIALLY TRANSPLANTED RAT MAMMARY TUMORS INDUCED BY 7,12-DIMETHYLBENZ[A]ANTHRACENE.

Lee C, Lapin V, Oyasu R, Battifora H
Dept. Urology and Cancer Center, Northwestern Univ. Medical Sch., Chicago, IL, 60611
Eur J Cancer Clin Oncol; 17(7):801-808 1981

Mammary tumors in inbred Fischer 344 female rats were induced by 7,12-dimethylbenz[a]anthracene (DMBA). Primary tumors were excised and transplanted sc to syngeneic recipients. The transplanted tumors, thus developed, were used for further serial transplantation of up to five passages. Transplanted Tumors were able to grow to 1.5-2 cm in diameter within 1-2 mo. Histologically, tumor tissues of early passages were characterized by mixed populations of epithelial and spindle cells while tumors of late passages contained only the spindle cells. Tumors grafted into ovariectomized hosts were not able to grow, although they remained viable, since estrogen therapy was able to activate their growth. By the third passage, tumors were able to grow when transplanted into ovariectomized recipients but the growth rate was considerably slower than that in the intact hosts. In the fourth and fifth passages, tumors transplanted in ovariectomized recipients grew as well as those in intact hosts. Following the establishment of the transplanted tumors, ovariectomy in the hosts resulted in an initial regression and subsequent regrowth of tumors of early passages and had no effect on those of late passages. The long-term growth of transplanted tumors in ovariectomized hosts was associated with an increase in the spindle cell population which gradually replaced the regressed epithelial cells. Results suggest that the so-called 'hormone-dependent' DMBA-induced mammary tumors consist of at least two histologically and biochemically distinct cell types, hormone-dependent epithelial and hormone-independent spindle-shaped cells, and that the latter are selected over the epithelial component during serial transplantations or under unfavorable hormonal conditions due to ovariectomy in the hosts. (26 Refs)

17. INFLUENCE OF THE ESTROUS CYCLE DURING CARCINOGEN EXPOSURE ON NITROSOMETHYLUREA-INDUCED RAT MAMMARY CARCINOMA.

Lindsey WF, Das Gupta TK, Beattie CW
(c/o Beattie) Div. Surgical Oncology, Univ. Illinois Medical Center, 840 South Wood St., Chicago, IL, 60612
Cancer Res; 41(10):3857-3862 1981

The influence of individual stages of the rat estrous cycle during exposure to l-nitroso-l-methylurea (NMU) on mammary tumor incidence, latency, number, and cytosol receptor dynamics for estrogen and progesterone was determined. Virgin female Buffalo rats were separated into three groups on day 53 according to their vaginal smear pattern. NMU (5 mg/100 g body wt, iv) was administered in 3 mo doses beginning at 53 to 55 days of age on diestrus, proestrus, or estrus between 9:00 and 11:00 a.m. Groups of rats had their second and third injections of NMU on the same day of the estrous cycle as their initial injection. All animals were killed during the morning on a diestrus day. Receptors for estrogen and progesterone were determined by a modified dextran-coated charcoal method and by sucrose density gradient analysis. Mean latencies to first tumor appearance in diestrus, proestrus, and estrus groups were 104.4, 83.6, and 91.4 days, respectively (p less than 0.05, diestrus versus estrus and proestrus) following the NMU injection. The mean number of tumors per rat was significantly higher in rats injected on proestrus (4.5) or estrus (4.3) than on diestrus (2.0). Estradiol bound to receptor sedimented at 8 and 4 s and was suppressed by diethylstilbestrol and estradiol. Progesterone receptor migrated to 7.8 and 4 s regions. Estrogen receptor incidence (100%) and content (16.7 fmol/mg cytosol protein) was highest in rats injected on diestrus. In the proestrus and estrus injected groups, estrogen receptor incidence was 95 and 63% and content was 10.2 and 11.2 fmol/mg protein, respectively. The affinity of estradiol for its receptor was not significantly altered in any group. Although there were no statistically significant differences in progesterone receptor incidence or affinity between groups, progesterone receptor content (74.6 fmol/mg cytosol protein) was significantly higher in tumors from rats injected on proestrus than on diestrus. These data suggest that the prevailing hormonal milieu of the estrous cycle during NMU exposure may be critically important to the subsequent biological behavior and steroid receptor status of carcinogen-induced rat mammary tumors. (Author abstract) (41 Refs)

18. LONG-TERM EFFECTS OF PERINATAL EXPOSURE TO 5ALPHA-DIHYDROTESTOSTERONE ON NORMAL AND NEOPLASTIC MAMMARY DEVELOPMENT IN MICE.

Yanai R, Nagasawa H, Mori T, Nakajima Y
Pharmacology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1 Chuo-ku, Tokyo 104, Japan
Endocrinol Jpn; 28(2):231-234 1981

Previous published observations of the effects of neonatal treatment with various aromatizable and nonaromatizable androgens and with 5beta-dihydrotestosterone (5b-DHT) in particular prompted this study of prenatal and neonatal treatment with 5alpha-dihydrotestosterone (5a-DHT) on mammary and pituitary growth and function. Pregnant SHN mice (a high mammary tumor strain) were given daily sc injections of 1 mg 5a-DHT dissolved in 0.1 ml olive oil 4 x on days 12-15 of pregnancy (prenatal treatment; 22 mice). Newborn mice from untreated mothers received 200 ug 5a-DHT/day sc in 0.02 ml olive oil 5 x on days 1-5 after birth (neonatal treatment; 30 mice). On the afternoon of estrous at 4 mo of age, five mice from each group were bled and sacrificed for laboratory examination; the remaining mice were followed until 9 mo of age for tumor development. No effect of treatment on body wt was seen in any group. Neonatal treatment with 5a-DHT resulted in significantly higher anterior pituitary wt and lower adrenal and ovarian wt than in the controls, and histological appearance of the ovaries was abnormal; prenatal treatment did not have these effects. Neonatal treatment resulted in a significantly higher incidence of mammary tumors at 5, 6, 7 and 9 mo of age (p less than 0.01-0.02), with final tumor incidences of 25/25 and 13/17 in the neonatal and prenatal treatment groups, respectively. The mice treated neonatally had significantly higher plasma prolactin level (199 +-13 nanog/ml) than did controls (51 +-9 nanog/ml), but pituitary prolactin content and concentration were similar; prenatal treatment did not affect these parameters. These results indicate that the long-term effects of perinatal treatment with 5b-DHT on normal and neoplastic mammary growth and pituitary prolactin secretion are much more marked than are the effects of 5a-DHT treatment. (8 Refs)

19. DIFFERENTIAL EFFECTS OF SELENIUM ON THE GROWTH OF MOUSE MAMMARY CELLS IN VITRO.

Medina D, Oborn CJ
Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Lett; 13(4):333-344 1981

The differential effects of selenium (present as Na2SeO3) on the growth of mammary cells in primary cultures and in established epithelial cell lines of mammary origin are reported. Primary monolayer cultures were obtained from BALB/cCrlMed mice (preneoplastic and adenocarcinoma tissue was derived from hyperplastic D2 and C4 cell line mammary transplants into syngeneic mice), and the established mouse mammary cell lines CL-S1, WAZ-2t, and YN-4 were used. Cultures were analyzed for DNA content and by cell count 4-7 days after selenium exposure began. Selenium at 5 x 10(-8) M stimulated primary cell culture growth of normal mammary, C4 preneoplastic, and YN-4, but not D2 preneoplastic, D2 tumor, CL-S1, and WAZ-2t cells. YN-4 and CL-S1, apparently representing selenium responsive and non-responsive mammary cell populations, showed differential dose sensitivities: 5 x 10(-8) M selenium stimulated YN-4 but not CL-S1, whereas 5 x 10(-5) M (toxic level) selenium completely inhibited but did not kill the YN-4 and CL-S1 cells. The two cell lines could be used in a model system for selenium studies. (36 Refs)

20. EFFECT OF DIETARY AMINO ACIDS ON TUMOUR GROWTH AND CELL-MEDIATED IMMUNE RESPONSES.

Bounous G, Sadarangani C, Pang KC, Kongshavn PA
Centre Hospitalier Universitaire, Sherbrooke PQ J1H 5N4, Canada
Clin Invest Med; 4(2):109-115 1981

The effects of various diets were studied in C3H/NCrlBR, C57Bl/6, and (AxC57Bl/6)F1 mice. Diet 1, the standard defined-formula amino acid diet, contained about the same amino acid distribution as casein. Diet 2 contained reduced amounts of l-methionine, l-phenylalanine, and l-tyrosine, and no cystine. Diet 3 contained almost double the amount of amino acids found in diet 1. The Puria mouse chow used contained approx 18% protein. Diet 1 supported normal growth in C3H/NCrlBR mice. Diet 3 and Purina did not produce more body growth than diet 1. Diet 2 produced impaired body growth and reduced spleen wt and WBC counts. Skin grafts were rejected sooner on mice fed diet 2 than on mice fed diet 1. Mice fed diet 2 had higher resistance to Listeria monocytogenes infection than those fed diet 1 or Purina. Diet did not affect the time of appearance of palpable fibrosarcomas. Palpable mammary adenocarcinomas appeared soonest in mice fed diet 3 or Purina. Diets 1 and 2 had about the same inhibitory effect on fibrosarcoma growth. Diet 2 had a greater inhibitory effect on the growth of mammary adenocarcinomas. Tumor growth showed a direct dose-response relationship to amino acid content of the diet. Graft-vs-host reactivity was not affected by diet. Evidently reduction of amino acid inhibits tumor growth, while excessive amino acids promotes tumor growth. This suggests that current concepts of 'good nutrition' promoting immune defenses may be in error. (26 Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

21. THE HORMONAL REGULATION AND INTERACTION OF CONCANAVALIN A AND INSULIN BINDING IN R3230AC MAMMARY ADENOCARCINOMA CELLS.

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Biochim Biophys Acta; 676(2):187-198 1981

To investigate the effects of concanavalin A on insulin binding to R3230AC mammary carcinomas, initial experiments were performed to characterize binding of concanavalin A. Concanavalin A binding was found to be specific and saturable. Equilibrium binding experiments demonstrated that addition of low concentrations of concanavalin A enhanced the binding of concanavalin A, suggestive of positively cooperative interactions. Binding of concanavalin A was responsive to hormonal alterations; tumor cells from diabetic rats showed enhanced binding of [3H]concanavalin A and insulin compared to cells from intact rats and administration of insulin to diabetic rats returned concanavalin A and insulin binding to levels seen in controls. Incubation of tumor cells with concanavalin A prior to addition of 125I-labeled insulin resulted in a reduction of insulin-binding capacity; succinyl-concanavalin A did not affect binding of insulin. The percent inhibition of insulin binding by concanavalin A was highest at the lower insulin concentrations, providing a linearized Scatchard plot that yielded a calculated Kd value comparable to the low-affinity portion of the curvilinear Scatchard plot for insulin binding. The dissociation rate of bound insulin depended on receptor occupancy. Addition of concanavalin A after insulin binding reached equilibrium resulted in increased insulin binding at higher hormone concentrations, decreased rates of dissociation of insulin and a loss of the correlation between receptor occupancy and dissociation rates. Concanavalin A alone demonstrated an insulin-like effect on glucose transport, which in these tumor cells represents a decrease in transport of 3-O-methylglucose. These results suggest that binding of both concanavalin A and insulin to cells from this hormonally responsive neoplasm is under insulin regulation and demonstrates similar characteristics to those reported for a variety of normal cells. Furthermore, the interaction between concanavalin A and the cell membranes affects the affinity of the insulin receptor for insulin and appears to decrease the observed negative cooperativity. (Author abstract) (58 Refs)

22. SYNTHESIS OF IMMUNOREACTIVE INSULIN IN VITRO BY APLASTIC MAMMARY CARCINOMA PRECONDITIONED IN DIABETIC MICE.

Pavelic K, Ferle-Vidovic A, Osmak M, Vuk-Pavlovic S
Rudjer Boskovic Inst., P.O. Box 1016, Bijenicka 54, 41001 Zagreb, Croatia, Yugoslavia
JNCI; 67(3):687-688 1981

Direct evidence is presented that the murine aplastic carcinoma, preconditioned in diabetic mice, secreted immunoreactive insulin (IRI) in vitro for at least 25 days. The intensity of in vitro IRI secretion depended on the length of the in vivo preconditioning. (Author abstract) (8 Refs)

23. INHIBITION OF DNA SYNTHESIS IN MOUSE EPIDERMIS AND BREAST EPITHELIUM BY DEHYDROEPIANDROSTERONE AND RELATED STEROIDS.

Pashko LL, Schwartz AG, Abou-Gharbia M, Swern D
Fels Res. Inst., Temple Univ., Philadelphia, PA, 19140
Carcinogenesis; 2(8):717-721 1981

Male ICR mice and female virgin C3H-A/A mice were treated with dehydroepiandrosterone (DHEA), DHEA-sulfate, DHEA-sulfatide, 16alpha-Br-epiandrosterone (Br-Epi), estradiol-17beta, progesterone, testosterone, or corticosterone. The activity of glucose-6-phosphate dehydrogenase (G6PDH) and the level of incorporation of [3H]thymidine in male mouse epidermis was determined. Incorporation of [3H]thymidine was also measured in female mouse breast epithelium. DHEA and DHEA-sulfatide significantly inhibited G6PDH activity in the epidermis. DHEA-sulfate had no inhibitory effect. Br-Epi was the most active inhibitor of the steroids tested. DHEA and DHEA-sulfatide inhibited the stimulation of [3H]thymidine incorporation by 12-O-tetradecanoylphorbol-13-acetate (TPA) in mouse epidermis. DHEA-sulfate did not have this effect. Br-Epi was much more potent an inhibitor in both the epidermis and breast epithelium than DHEA. Of the sex steroids tested, only corticosterone inhibited TPA-stimulated incorporation of [3H]thymidine. The results indicate that the activity of DHEA, which has been shown to suppress spontaneous breast c ancer development in mice, is not limited to breast epithelium. A possible relationship to spontaneous breast cancer in humans is suggested. (25 Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

24. DEMONSTRATION WITH MONOCLONAL ANTIBODIES OF AN UNUSUAL MONONUCLEAR CELL INFILTRATE AND LOSS OF NORMAL EPITHELIAL MEMBRANE ANTIGENS IN HUMAN BREAST CARCINOMAS.

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Lancet; 2(8244):434-438 1981

Monoclonal antibodies to two differentiation antigens normally expressed on the membranes of breast epithelial cells were used in immunofluorescence studies on frozen sections of malignant breast tumors. It was demonstrated that most tumors did not express these antigens on their cell membranes, and it was possible to classify histologically indistinguishable tumors according to whether they expressed the antigens. The absence of these membrane antigens is likely to be a subtle indicator of cellular differentiation and to have metabolic and other functional implications for the tumor. The demonstration that otherwise indistinguishable tumors can be classified in this way therefore has obvious potential for clinical exploitation. In addition, it was demonstrated that the majority of the mononuclear cells in those tumors with intense mononuclear cell infiltrates expressed an antigen not normally found on mature lymphocytes and macrophages. (Author abstract) (11 Refs)

25. PROGNOSTIC VALUE OF CONCANAVALIN A REACTIVITY OF PRIMARY HUMAN BREAST CANCER CELLS.

Furmansk P, Kirkland WL, Gargala T, Rich MA, Breast Cancer Prognostic Study Clinical Associates
Dept. Biology, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 41(10):4087-4092 1981

A prospective, double-blind study was carried out to determine whether reactivity with concanavalin A (Con A) of human breast cancer cells was related to early disease recurrence. Mammary epithelial cells were isolated from 138 primary human breast cancers. The cells were placed in culture, and their reactivity with Con A was determined with a hemadsorption assay in which human RBC treated with various concentrations of Con A were incubated with the test (mammary epithelial) cells in situ. The Con A half-max value was determined as the concentration of Con A at which approx 50% of the target cells adsorbed RBC. Con A reactivity of the tumors was classified as high or low (half-max value less than or equal to 30 or greater than 30 ug/ml, respectively). Patients were followed for 2 to 60 mo after primary surgery (median, 22 mo). Those patients having tumors that were highly reactive with Con A were at significantly greater risk of developing early recurrence of their cancers than were those patients with low-reactivity tumors. No correlation was found between Con A reactivity and the age of the patients, their menopausal status, the number of axillary lymph nodes infiltrated with tumor, the estrogen receptor content of the tumor, or the clinical stage of the disease. These data show that Con A reactivity is an independent discriminator for identifying those breast cancer patients who are at high risk of developing early recurrent disease. (Author abstract) (28 Refs)

26. CHANGES IN INTERFERON AND THYMUS FACTOR LEVELS AS WELL AS IN LYMPHOCYTE POPULATIONS IN PATIENTS WITH MAMMARY CARCINOMA.

Busse E, Rose H, Helmholz M, Kaiser E, Riessbeck KH
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Zentralbl Gynaekol; 103(12):694-702 1981

Changes in interferon and thymus factor as well as in cAMP levels and WBC populations were recorded from patients with mammary carcinoma. They were equally recordable from those in whom no clinical tumor had been detectable at the time of postsurgical examination as well as from patients with metastases distant from the primary tumor. The possibility for centralized disorder of immunological tumor cell defense in carcinoma patients is discussed. (Author abstract) (68 Refs) (In GER)

27. ANALYSIS OF SERA FROM BREAST CANCER PATIENTS BY RADIOIMMUNOASSAYS.

Davis JW, Olive M, Cailleau R, Bowen JM
Dept. Molecular Carcinogenesis and Virology, Texas Medical Center, Univ. Texas System Cancer Center, MD Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Immunol Immunother; 11(3):225-231 1981

Sera from 324 breast cancer patients were tested against various cell lines, including four human breast cancer, four human non-breast cancer, and three animal cell lines. Antibody reactivity was measured indirectly by binding antibodies to I125-labeled protein and directly using I125-labeled antibodies. Sera from 30 patients showed positive results, with nine different patterns of reactivity. Of these sera, two samples reacted positively only to human breast cell lines MDA-MB231 and MDA-MB330. Fifteen of the remaining 28 samples reacted with animal as well as human cell lines. Evidently breast cancer patients are sensitized to antigens occurring on breast cancer cells more often than normal individuals. Several different types of antigens, not all of which are specific to breast cancer cells, are detected by sera from such patients. The types of sera reactive only against breast cancer cell lines may be useful for the analysis of tumor-associated antigens. (36 Refs)

28. INCREASED DETECTION OF MAMMARY CARCINOMA CELLS IN MARROW SMEARS USING ANTISERA TO EPITHELIAL MEMBRANE ANTIGEN.

Dearnaley DP, Sloane JP, Ormerod MG, Steele K, Coombes RC, Clink HMcD, Powles TJ, Ford HT, Gazet J-C, Neville AM
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Br J Cancer; 44(1):85-90 1981

We have developed a technique for the immunocytochemical staining of marrow smears using antiserum to epithelial membrane antigen (EMA). This membrane component is confined to, but widely distributed in, epithelial tissues and tumors derived from them, and is strongly expressed by infiltrating breast carcinoma cells. Marrow aspirates from patients with both early and metastastic breast cancer have been examined, and the results of immunocytochemical staining compared with conventional cytology and histology. Staining with antiserum to EMA enabled us to detect small numbers of carcinoma cells, and increased the yield of positive samples. Furthermore, using this technique, we found malignant cells in the marrow of patients with primary breast cancer with no other evidence of metastastic disease. Thus immunocytochemical staining for EMA may be of value in the detection of micrometastases in patients with primary breast carcinoma. (Author abstract) (13 Refs)

29. MEDULLARY CARCINOMA OF BREAST: AN IMMUNOHISTOCHEMICAL STUDY OF ITS LYMPHOID STROMA.

Hsu SM, Raine L, Nayak RN
Lab. Pathology, NCI, NIH, Bethesda, MD, 20205
Cancer; 48(6):1368-1376 1981

Immunoperoxidase staining for IgA, IgG, IgM, and secretory component (SC) was performed on 10 cases each of medullary carcinoma and infiltrating duct carcinoma of the breast. Plasma cell-rich stroma of medullary carcinoma was found to contain predominantly IgA plasma cells. Tumor cells also contained IgA and SC. In contrast, the few plasma cells of infiltrating duct carcinoma were found to be predominantly IgG type, and the tumor cells contained none or very small amounts of IgA and SC. Because the presence of IgA plasma cells and IgA and SC in lining epithelial cells are characteristic features of organs of the secretory Ig system, these findings in medullary carcinoma may suggest a good degree of functional differentiation of these tumor cells and correlate well with the well-known favorable prognosis associated with this tumor. (Author abstract) (34 Refs)

30. INHIBITION OF MACROPHAGEAL TRANSFORMATION OF MONONUCLEAR CELLS OF PERIPHERAL BLOOD IN BREAST CANCER.

Dzhaginian AI, Demchenko TA
Medical Inst. Sanitation and Hygiene, Leningrad, USSR
Vopr Onkol; 27(6):32-35 1981

Macrophageal transformation of mononuclear cells of peripheral blood was evaluated quantitatively in vitro. The study group included 60 patients with breast cancer Stage II-IV and 50 healthy subjects. Transformation of mononuclear cells to macrophages in breast cancer patients, particularly in advanced cases, was found to be reduced, as compared with healthy controls. The serum of cancer patients contains an inhibitor of this process. This was confirmed by mononuclear cell transformation being inhibited both in patients and controls on addition of the serum of cancer patients to both cultures. The function of tumor patients' cells was partially restored, when serum of healthy controls was added. It is suggested that macrophageal transformation be used as a test for immunologic examination of tumor patients. (Author abstract) (13 Refs) (In RUS)

31. DISTRIBUTION OF HLA CLASS 1 ANTIGENS IN NORMAL HUMAN TISSUE AND IN MAMMARY CANCER.

Fleming KA, McMichael A, Morton JA, Woods J, McGee JO'D
(c/o McGee) Nuffield Dept. Pathology, John Radcliffe Hosp., Headington, Oxford OX3 9DU, England
J Clin Pathol; 34(7):779-784 1981

With a monoclonal antibody which reacts with all HLA Class 1 antigens it was found that these antigens are not uniformly distributed in all nucleated cells. Rather HLA Class 1 antigens are restricted in their distribution to lymphoid cells, endothelial cells of small vessels, and certain epithelia including mammary duct cells. These antigens were not detected on hepatocytes, specialized cells of the central nervous system, or on the tumor cells of 8 out of 17 human mammary cancers. Given the hypothesis that T cells only respond to foreign antigens on cells which share a common major histocompatibility antigen, these results imply that the T cell responses to viral infections of hepatocytes - for example, hepatitis B virus and the CNS - for example, subacute sclerosing encephalitis, are mediated through an antigen system other than HLA Class 1. The absence of HLA Class 1 antigen on many mammary cancer cells may be of prognostic significance if T cell modulation of tumor growth is mediated through this class of antigens. (Author abstract) (19 Refs)

32. ONCOFETAL ANTIGEN-I: DISTRIBUTION IN HUMAN TUMORS.

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JNCI; 67(3):557-562 1981

Oncofetal antigen-l (OFA-l) is a human tumor-associated fetal antigen that cross-reacts with fetal brain. The biological distribution of this antigen was studied in a variety of histologic types of human tumors and normal tissues. A total of 170 human tumors and 89 normal tissues obtained from biopsied and autopsied specimens were tested by immune adherence absorption assay. The antigen was most prevalent in malignant melanomas (82%); next in order of incidence were lung carcinomas (71%), sarcomas (61%), brain tumors (58%), and breast carcinomas (53%). However, OFA-I was found in only 15% of gastrointestinal tumors. The four hepatoma specimens tested were negative for OFA-I. OFA-I was also present in metastases and normal-appearing tissues of patients with OFA-I positive tumors but was not found in normal tissues from noncancer patients. These studies demonstrated that OFA-I is widely distributed among human tumors. It appears to be more prevalent in tumors of ectodermal and mesodermal origin. (Author abstract) (34 Refs)

33. NATURALLY ARISING TUMORS OF THE INBRED WAB/NOT RAT STRAIN. II. IMMUNOGENICITY OF TRANSPLANTED TUMORS.

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Dept. Chemical Pathology, Royal Liverpool Hosp., Prescot St., Liverpool, L7 8XP, England
JNCI; 67(3):637-643 1981

The immunogenicity of 28 transplanted naturally arising tumors of the inbred WAB/Not rat was investigated at early passages in strictly syngeneic, contemporary animals. Included were nephroblastomas, histologically benign and malignant mammary tumors, soft tissue and skin tumors, one lymphoid tumor, and two gastrointestinal lesions. In no case was evidence of immunogenicity observed when animals were treated with multiple grafts of irradiated (15,000 rad) tissue or by excision of a growing tumor. A few of these tumors were further investigated by other methods of immunization, including injection at various sites of irradiated cells followed by challenge at different sites and multiple injections of mitomycin C- or Formalin-treated cells. Again no evidence of immunogenicity was seen. Attempts to immunize with viable cells mixed with BCG or Corynebacterium parvum failed due to lack of tumor suppression by these agents. Limited concomitant immunity experiments yielded similarly negative results, except in one case of a fibrosarcoma for which a slight reduction in second tumor growth was observed when primary implants were very large. Some alterations in biologic properties during transplant passage and the incidence of post-excision recurrence and metastatic spread of some of the tumors are described. (Author abstract) (21 Refs)

34. PREFERENTIAL GROWTH OF MAMMARY TUMORS IN INTACT MAMMARY FATPADS.

Miller FR, Medina D, Heppner GH
Dept. Immunology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
Cancer Res; 41(10):3863-3867 1981

Four transplantable mammary tumors, three (66, 410, and 168cl) isolated from a spontaneously occurring strain BALB/cfC3H mammary tumor and one (D2) arising from a BALB/c hyperplastic alveolar nodule were found to grow better in mammary fatpads than at sc sites. Furthermore, tumor growth was better (p less than 0.05) in intact mammary glands than in cleared mammary fatpads from the D2, 410, and 66 tumors (168cl was not tested). The role of immunity in these differences was investigated using the highly immunogenic 410 tumor. Tumor 410 induced equally effective immunity to subsequent challenge whether it was implanted sc or in intact fatpads. Furthermore, in immunized animals, Tumor 410 was rejected equally well when the challenge site was intact fatpad as when sc. Similarly, Tumor 410 induced immunity after implantation into cleared fatpads and, in immunized animals, were rejected when the challenge site was the cleared fatpad. We thus found no evidence that the mammary fatpad is immunologically privileged, as compared to the sc site, with respect to tumor transplantation antigens. (Author abstract) (21 Refs)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

35. MAMMARY TUMOR VIRUS PROVIRAL DNA IN NORMAL MURINE TISSUE AND NON-VIRALLY INDUCED MAMMARY TUMORS.

Michalides R, Wagenaar E, Groner B, Hynes NE
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J Virol; 39(2):367-376 1981

The Southern DNA filter transfer technique was used to study the involvement of the endogenous mouse mammary tumor virus (MMTV) in the development of mammary tumors of nonviral etiology. The presence of extra MMTV proviruses in the genomes of these non-virally induced mammary tumors would indicate an integration of the provirus of an activated endogenous MMTV. Acquisition of MMTV proviruses did not seem to be an absolute requirement for the development of hormone or carcinogenically induced mammary tumors in strain BALB/c nor for hormone-induced mammary tumors in mouse strains 020, C57BL, and C3Hf. In some hormone-induced mammary tumors we did observe extra MMTV proviruses in submolar quantities, indicating that reintegration may occasionally occur and that only a part of the tumor cells acquired new MMTV DNA information. Hormone-dependent and -independent primary mammary tumors of the mouse strain GR, which are controlled by the Mtv-2 mammary tumor induction gene, all acquired extra MMTV proviruses. Most of these extra MMTV proviral-DNA-containing fragments appeared present in submolar quantities, suggesting that only part of the tumor cells acquired extra MMTV proviral information. These findings indicate that the initially transformed mammary gland cells of non-virally induced mammary tumors do not necessarily acquire extra MMTV proviral DNA information, in contrast to the MMTV-induced mammary tumors, in which all tumor cells contain extra MMTV DNA information. (Author abstract) (34 Refs)

36. ISOLATION AND CHARACTERIZATION OF A NEW MOUSE MAMMARY TUMOR VIRUS FROM BALB/C MICE.

Drohan W, Teramoto YA, Medina D, Schlom J
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Virology; 114(1):175-186 1981

A novel mouse mammary tumor virus (MMTV) has been isolated from mice of a subline of the BALB/cCrl Med mouse strain designated BALB/cV. Whereas breeding females of the parent BALB/cCrl Med colony have a mammary tumor incidence of 1%, 47% of the breeding females of the BALB/cV subline develop mammary tumors before 10 mo of age. Foster nursing experiments demonstrated this virus, termed MMTV (BALB/c), was transmitted only by milk. The novel MMTV isolate was shown to be immunologically related to, but distinct, from the MMTV variants of C3H, GR, and RIII mice by a series of competition radioimmunoassays for the MMTV 28,000-dalton major core protein (p28), and the 52,000 (gp52)- and 36,000-dalton (gp36) major envelope glycoproteins. Monoclonal antibodies directed against MMTV gp36 were also used to clearly distinguish MMTV(BALB/c) from MMTV(C3H), MMTV(RIII), MMTV(GR) MMTV(C3HfC57BL), and MMTV(A). MMTV-specific proviral DNA content of mammary adenocarcinomas arising in the BALB/cV subline was examined with restriction endonucleases and the Southern blot technique, and compared to the MMTV proviral DNA content of BALB/cAnDe mammary tumors. The virus arising from these latter tumors has been termed MMTV(O). Analysis of EcoRI digests of high-mol-wt DNA from both types of mammary tumors demonstrated additional MMTV-related proviral sequences when compared to the DNA of normal BALB/c tissues. The patterns generated with the restriction endonuclease SacI distinguished the additional MMTV-specific proviral information in the mammary tumors of the BALB/cV mice from the proviral information in tissues containing the GR, C3H, or RIII MMTVs, as well as from the proviral information in the BALB/cAnDe mammary tumors. These immunological and molecular studies thus define MMTV(BALB/c) as a novel MMTV variant. (Author abstract) (38 Refs)

37. ESTABLISHMENT OF CULTURED DD/TBR MOUSE MAMMARY TUMOR CELL LINES.

Iwai Y
Central Res. Inst., Radiation Center of Osaka Prefecture, Osaka, Japan
Nara Igaku Zasshi; 32(2):168-180 1981

Three mouse mammary gland cultured cell lines were established from a mammary carcinoma that spontaneously occurred in a 10-mo-old female DD/Tbr strain mouse. Two of the cell lines were epithelial (DD-762 and DD-763) type cells and one was spindle-shaped (DD-761). Except for the DD-764 cell line, the chromosome number was 80 and the population doubling time was 18 hr. These cell lines were thought to produce B-type RNA virus (MuMTV) and not murine leukemia virus (MuLV). Study of viral kinetics by means of RNA-directed DNA polymerase (RDDP) activity assay indicated that MuMTV production was observable during the stationary phase but not the logarithmic phase of cell growth. The production of the mammary tumor virus was found to be inversely dependent upon the presence of dexamethasone (DXM); MuMTV was produced in large amounts (0.8 mg viral protein/liter/day in DD-764), and the production was enhanced with the addition of DXM. (27 Refs) (In JPN)

38. QUANTITATION OF VIRAL ANTIGENS RELEASED INTO PLASMA AND CULTURE FLUIDS BY MURINE MAMMARY TUMOR CELLS.

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Univ. Tennessee Center for Health Sciences, Memphis, TN, 38163
Cancer Res; 41(10):3885-3890 1981

Radioimmunoassays capable of measuring mouse mammary tumor virus (MMTV) mol wt 52,000 envelope glycoproteins (gp52) and mol wt 27,000 proteins (p27) have been used to quantitatively compare plasma concentrations of these viral antigens in mice bearing spontaneous mammary tumors. Although gp52 was detected in the plasma of all tumor-bearing mice tested, p27 was detected in only a portion of tumor-bearing animals. In p27-positive animals, gp52 was detected in higher concentrations than p27. These findings demonstrate that gp52 has preferential utility as a plasma marker for the presence of mammary tumors in MMTV-infected hybrid (BALB/c x DBA/8 F1), Paris RIII, and C3H/HeJ mice. In addition, cultures of MMTV-producing cells [GR-MMTV and MMTV(C3H)Fe1] were used as models to study the release of viral antigens in the absence of serum antibody or additional host factors. Comparisons of extracellular soluble and particulate antigen concentrations demonstrated that gp52 and p27 were present in substantially higher concentrations as soluble than virion-associated antigens. The mean ratio of non-virion-associated gp52 to virion-associated gp52 was 12:5:1 for GR-MMTV cells and 37:3:1 for MMTV(C3H)Fe1 cells. The marked stability of MMTV in culture fluids suggested that virion breakdown was not responsible for the accumulation of soluble viral antigens in culture. The information obtained suggests that abundant virus-free antigens may be of greater use than virion-associated antigens as a source of viral antigen to evaluate mammary tumor status. (Author abstract) (20 Refs)

39. ESTIMATION OF MOUSE MAMMARY TUMOR VIRUS GP52 ABUNDANCE BY PROTEIN A ASSAY: A COMPARISON OF VIRAL ANTIGEN EXPRESSION ON C3H AND GR MAMMARY TUMOR CELLS.

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Intervirology; 15(2):111-120 1981

An adherent cell isotopic staphylococcal protein A test (ISPAT) was used to estimate the abundance of mouse mammary tumor virus (MMTV) gp52 cell surface antigen (CSA) on mammary tumor cells. Protein A assays were first utilized, not strictly as a means of antigen detection, but as a means to determine the kinetics of dexamethasone-mediated changes in gp52 cell surface expression. Results indicated increases in gp52 CSA within 4 hr of dexamethasone treatment and max levels of antigen expression within 12-24 hr after treatment. Comparison of gp52 determinants on dexamethasone-stimulated mammary tumor cells demonstrated a greater abundance on C3H Mm5mt/cl than on GR-MMTV cultures. Parallel antigen assays with gp52 and Rauscher murine leukemia virus (R-MuLV) antisera demonstrated that GR-MMTV cells expressed fewer C-type determinants and thus a more preferential expression of gp52 determinants than other cell lines tested. The gp52/R-MuLV binding ratio was only 2.4:1 for C3H cultures in contrast to 5.7:1 for GR cultures. In addition, a comparison of gp52 expression on viral producer and nonproducer cells provided a quantitative estim ate of the extent of expression which occurred in a retrovirus nonproducer culture. Results of ISPAT demonstrated that 75% of the gp52 detected on producer cells was present on nonproducer cultures. Comparison of the expression of gp52 CSA and the release of gp52 into culture fluids during hormone treatments demonstrated that both assays (ISPAT and gp52 radioimmunoassay) detect and quantitate coordinate changes in the expression and release of MMTV gp52. In antibody excess, protein A assays provided quantitative estimates of CSA abundance not offered by alternative methods of CSA detection. (Author abstract) (17 Refs)

40. POSSIBLE ASSOCIATION BETWEEN ONCOGENIC VIRUSES AND HUMAN BREAST TUMORS.

Il'in KV, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (7):10-18 1981

Literature data on the association between human breast tumors and at least two oncogenic viruses are reviewed. Immunodiffusion with autoradiography showed the presence of protein with antigenic determinant similar to that of antigen p27 in 11/23 breast fibroadenoma specimens. The specimens of malignant breast tumors did not contain the antigenic determinant of simian virus type D. The specimens of human breast carcinoma were found to contain the antigen similar to the major envelope protein gp52 of murine virus of mammary gland. The presence of gp52 antigen was not correlated either with the age of the patient or with the histology of the tumor. (48 Refs) (In RUS)

RADIOLOGICAL ASPECTS OF MAMMARY GLAND CARCINOGENESIS

41. RADIATION RESPONSE OF AUTOCHTHONOUS MAMMARY TUMORS IN SHN MICE.

Tanooka H, Tokuzen R, Tanaka K
Radiobiology Div., Natl. Cancer Center Res. Inst., Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan
Gan; 72(4):578-582 1981

The radiation response of spontaneously induced autochthonous mammary tumors was studied in SHN mice, a strain developed at the National Cancer Center. Tumors were mostly adenocarcinomas and grew with an av vol-doubling time of 3.0 days. When tumors reached a size of 8-10 mm in diameter, they were given a single, local irradiation with 6 MVp x-rays generated by a medical linear accelerator. With radiation doses lower than 2 krad, the tumors regrew after a temporary interruption. Surviving fractions of tumor cells in situ were estimated from the tumor regrowth times. yielding a survival curve with D0=480 rad for n=2. With 6.5 krad, tumor regression was very rapid: the vol-halving time was 1.7 days, and temporary tumor control was achieved. This rapid radiation response was not necessarily correlated with the radiosensitivity of tumor cells and is thought to be related to the structure of the mammary tumor mass. A disadvantage of this mouse strain was its high multiple tumor incidence which interfered with the observation of tumor control for adequate periods after irradiation. (Author abstract) (13 Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

42. HORMONE RECEPTORS IN MALE BREAST CARCINOMA.

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J Surg Oncol; 18(1):55-59 1981

It is well established that approx 60% of female breast cancers contain estrogen receptors (ER+). The hormonal receptor status of male breast cancers remains relatively unknown. Tumor tissue from 14 patients has been reviewed at the University of Oregon Health Sciences Center. Specimens of all 14 patients were ER+ with a range of 5.5 to 374 fmol/mg protein. Eight of 12 patients had tumors which also contained progesterone receptors (PR+) with a range of 42 to 1,852 fmol/mg/protein. Nine patients were treated by modified radical mastectomy, two by radical mastectomy, one by simple mastectomy, and two by biopsies only. Twelve patients remain free of disease with a mean follow-up of less than 2 yr. The two patients who developed metastases both responded to endocrine ablation by orchiectomy and subsequent adrenalectomy. These data suggest that male breast cancer is highly endocrine sensitive and that endocrine ablation can play an integral part in those men unfortunate enough to develop disseminated disease. (Author abstract) (18 Refs)

43. COMPARISON OF ESTRADIOL RECEPTOR INVESTIGATIONS AND HISTOCHEMICAL INVESTIGATIONS ON ENZYMES IN HUMAN MAMMARY CANCERS.

Gorlich M, Hecker D, Heise E
Dept. Experimental, Clinical Endocrinology, Central Inst. Cancer Res., Berlin, W. Germany
JNCI; 67(3):521-527 1981

The best way to predict the responsiveness of human breast carcinomas to hormone therapy is to investigate the estradiol receptor-binding abilities of these tumors. This binding induces many hormone-regulated changes in the activities of several enzymes. Therefore, enzyme activities after short-term organ culture exposed to added hormones were tested to see whether a correlation of enzyme activities exists with estradiol receptor binding. The results from both the estradiol receptor investigations and histochemical investigations on enzymes revealed a high degree of conformity, which confirms the existence of such a correlation. However, for this reason histochemical investigations on enzymes cannot eliminate the discrepancy between the experimentally verified existence of estradiol receptor binding and the response of mammary tumors to hormone therapy, which is not higher than 50-60%. (Author abstract) (19 Refs)

44. EVIDENCE THAT ESTROGEN-RECEPTOR-NEGATIVE, PROGESTERONE-RECEPTOR-POSITIVE BREAST AND OVARIAN CARCINOMAS CONTAIN ESTROGEN RECEPTOR.

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Cancer; 48(5):1215-1220 1981

A small number of primary metastatic breast carcinomas are estrogen-receptor-negative and progesterone-receptor-positive (ER-, PGR+) under the normal ligand-binding assay or sucrose density gradient conditions. Among more than 500 tumors analyzed in this laboratory over a yr and a half, 28 cases fit this category, 18 of which were patients 51 yr of age or younger (Group A) and 7 were patients over the age of 56 (Group B). The ages of three patients were unknown (Group C). By treatment of each of those tumor cytosols with dextran-coated charcoal before the assay was done, 13 of group A became positive (ER range 10-87 fmol/mg protein), 1 was borderline (ER 3-9 fmol/mg protein), 1 became positive only on sucrose gradient determination, and 2 remained negative. In comparison, two patients in Group B shifted from borderline ER to ER+ and only one ER- became ER+ at 10 fmol/mg protein. The data provide additional rationale for determining both ER and PGR in all patients, and have obvious implications for the need for standard methods of determining ER and PGR in the prognosis of women with breast cancer. (Author abstract) (19 Refs)

45. MEASUREMENT OF PROGESTERONE RECEPTORS IN HUMAN BREAST TUMORS: COMPARISON OF VARIOUS METHODS OF ANALYSIS.

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Dept. Lab. Medicine, Univ, Washington Sch. Medicine, Seattle, WA, 98195
J Steroid Biochem; 14(9):851-854 1981

The measurement of estrogen and progesterone receptors in human breast tumors is important to the successful management of the patients. These receptors exist in two macromolecular forms that have different sedimentation coefficients: 4S and 8S. Progesterone receptors were measured simultaneously in freshly prepared tissue cytosols from 10 individual tumors by three methods: the single-saturating dose (SSD) analysis, the sucrose density gradient method, and the multi-point Scatchard plot analysis. All three methods agreed extremely well for the determination of total (4S + 8S) receptor concentration; there was no loss of receptor-binding activity during the time required for sucrose density gradient analysis. The two macromolecular forms of the receptor appear to have similar if not identical dissociation constants because receptor concentrations calculated by extrapolation of linear Scatchard plots are identical to those obtained from either the summation of 4S and 8S areas of the density gradients or the SSD analysis. All three tested methods can be used in clinical measurements of the progesterone receptor. (14 Refs)

46. OESTROGEN RECEPTOR ASSAY AND MORPHOLOGY OF BREAST CANCER.

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Pathology; 13(2):317-325 1981

The associations between estrogen receptors, several morphological features and prognosis were studied in 53 cases of primary breast carcinoma. There was no significant association between estrogen receptors and any morphological property studied (histological grade, cellularity, fibrosis, elastosis, necrosis, lymphatic permeation, follicular hyperplasia, encapsulation, vascular invasion, tubular areas, histiocytosis, lymphocytic cell infiltration, number of invaded lymph nodes, tumor size, site of recurrence). Disease-free interval and survival were longer in patients having cancers with positive estrogen receptors. Good prognostic signs were low histological grades, tubular areas and absence of lymphatic invasion within the primary tumor. (Author abstract) (22 Refs)

47. STUDIES ON SPECIFIC MARKERS OF HORMONE-DEPENDENCE IN ENDOMETRIAL CARCINOMA: ESTRADIOL RECEPTORS AND UTERINE PEROXIDASE.

Morikawa S, Sekiya S, Takamizawa H
Dept. Obstetrics and Gynecology, Sch. Medicine, Chiba Univ., Inohana, Chiba 280, Japan
Nippon Sanka Fujinka Gakkai Zasshi; 33(3):339-343 1981

Both cytosol estradiol-17beta (E2) receptors and uterine peroxidase were detected in normal uterine tissues of rat and hamster, however, they were not detected when the tissues were cultivated in vitro. Uterine peroxidase was specifically induced by the administration of E2 in these normal uterine tissues in vivo. On the other hand, malignant tissues formed by the transplantation of uterine and mammary adenocarcinoma cells showed hormone-independence. Neither cytosol E2 receptors nor peroxidase were detected in these malignant tissues. These results indicate that, in addition to E2 receptors, peroxidase induction by E2 is a specific marker for hormone-dependence in both normal and abnormal uterine tissues. (Author abstract) (20 Refs) (In JPN)

48. THYROID HORMONE RECEPTORS IN HUMAN BREAST CANCER.

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Cancer Res; 41(10):4167-4173 1981

Optimum conditions were established for preparation of nuclei from human breast cancer biopsies. Incubation of nuclei with various concentrations of of L-3,3',5-[125I]triiodothyronine showed the presence of three binding systems: a high-affinity binding system (Type I) (KD approx 1.5 nM); an intermediate-affinity saturable system (Type II) (Kd approx 0.5 um); and a nonsaturable nonspecific system. Salt at high concentrations (0.4 M-KCl) extracted only Type I triiodothyronine-binding protein, thus simplifying its study and quantification. Type I binding protein was shown to have the affinity for triiodothyronine and the hormonal specificity usually ascribed to thyroid hormone receptors. Its sedimentation coefficient was 3.6S at 0.4 M KCl. Extractable triiodothyronine receptor was measured in 58 individual biopsies of primary and metastatic breast cancer. It was present in all tumors, but its concentration was highly variable (0.20 pmol/mg DNA; range, 0.044 to 0.702). Triiodothyronine receptor concentration was not correlated with age or endocrine status of the patient or with extension or histological grading of the tumor. Moreover, there was no correlation with estradiol and progesterone receptor concentrations. (Author abstract) (38 Refs)

49. 1,25-DIHYDROXYVITAMIN D3 SPECIFICALLY BINDS TO A HUMAN BREAST CANCER CELL LINE (T47D) AND STIMULATES GROWTH.

Freake HC, Marcocci C, Iwasaki J, MacIntyre I
Endocrine Unit, Royal Postgraduate Medical Sch., Du Cane Road, London, W12 OHS, England
Biochem Biophys Res Commun; 101(4):1131-1138 1981

The binding of the active vitamin D3 metabolite 1,25-dihydroxyvitamin D3 (DHD) to receptors on T47D breast carcinoma cells in vitro was studied. A specific receptor with a dissociation constant of 1.1 x 10(-10), a sucrose gradient sedimentation coefficient of 3.7S and a frequency of 15,000 sites/cell was identified. Growth of T47D cells was enhanced by DHD in a dose-dependent manner at physiological doses up to 0.8 nanoM. At higher doses the effect was eliminated. Growth was also enhanced by estradiol. Metabolites of vitamin D3 showing affinity for the binding sites, in decreasing order of affinity, were the 1,25-dihydroxy, 1,24,25-trihydroxy, 25 hydroxy, and 24,25-dihydroxy derivatives. The new metabolite 1beta,25-dihydroxyvitamin D3 had the same affinity as the 24,25 dihydroxy metabolite. The binding site was retained in culture cell lines from the parental tissue. The in vivo significance of vitamin D3 effects on breast cancer cells is unknown. (15 Refs)

50. EVIDENCE FOR TWO FORMS OF REVERSE TRANSCRIPTASE IN HUMAN PLACENTA OF A PATIENT WITH BREAST CANCER. PURIFICATION AND BIOCHEMICAL CHARACTERIZATION OF THE ENZYMES.

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Biochem J; 197(3):553-563 1981

Two DNA polymerases with properties of viral RNA-directed DNA polymerase were found in the placenta of a patient with breast cancer. Both enzyme activities were purified by column-chromatographic procedures or by preparative isoelectric focusing. The most distinguishing feature of the two enzymes is their specificity to transcribe (rA)n.(dT)12 or (rC)n.(dG)18. The two enzymes differ with respect to their elution profiles from the phosphocellulose column, isoelectric point, mol wt, bivalent-cation requirements and thermal stability. Serological analysis of the (rA)n.(dT)12-activated enzyme showed that this enzym e is immunologicaly not related to DNA polymerase-gamma, or to any of the reverse transcriptases purified from retroviruses of avian, murine and subprimate origin. However, the activity of this enzyme was neutralized by antibodies to reverse transcriptase purified from human spleen of a patient with myelofibrosis. Attempts to purify reverse transcriptase from normal human placenta were repeatedly unsuccessful. Once the crude homogenate of normal human placenta was freed from endogenous nucleic acids, no (rC)n.(dG)18-dependent activity could be detected. (Author abstract) (17 Refs)

51. FLOW CYTOMETRY OF BREAST CARCINOMA: I. RELATION OF DNA PLOIDY LEVEL TO HISTOLOGY AND ESTROGEN RECEPTOR.

Olszewski W, Darzynkiewicz Z, Rosen PP, Schwartz MK, Melamed MR
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Cancer; 48(4):980-984 1981

Flow cytometry studies of the DNA distribution of tumor cells from 92 human breast cancers showed measurable aneuploidy (hyperploidy) in 85 cases (92%). The DNA ploidy values were unimodal in each case, but there was a bimodal distribution for the entire series. One group of tumors had a diploid or near diploid DNA distribution and a second group had ploidy levels from triploid to tetraploid or higher. The tumors with lower DNA ploidy (at or near diploid) tended to be histologically low grade, cytologically more orderly and estrogen-binding positive; those with higher DNA ploidy were more likely to be higher grade, more anaplastic, and estrogen-binding negative. (Author abstract) (27 Refs)

52. FLOW CYTOMETRY OF BREAST CARCINOMA: II. RELATION OF TUMOR CELL CYCLE DISTRIBUTION TO HISTOLOGY AND ESTROGEN RECEPTOR.

Olszewski W, Darzynkiewicz Z, Rosen PP, Schwartz MK, Melamed MR
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Cancer; 48(4):985-988 1981

Flow cytometry analysis of cell cycle distribution was carried out on acridine-orange-stained cell suspensions freshly prepared from carcinoma of the breast of 90 women, and compared with control, benign breast specimens from 10 women. There was a significantly greater proportion of cells in S (9.1% +-5.8) and G2 + M (8.0 +-6.0) phases of the cycle in breast cancer specimens than in the S (1.5% +-0.6) and G2 + M (2.5 +-0.9) phases of the cycle in benign, control specimens of breast tissue. Great variation was noted among the breast cancers, with medullary carcinomas having the highest percentage of cells in S + G2 + M, and papillary, tubular, colloid and well-differentiated duct carcinomas having the lowest. Tumors from premenopausal women classified as estrogen receptor negative had significantly more cells in S + G2 + M than did tumors from postmenopausal women that were estrogen-receptor positive. (Auth or abstract) (13 Refs)

53. GAMMA-GLUTAMYLTRANSFERASE, A COMMON MARKER OF HUMAN EPITHELIAL TUMORS?

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Cancer Detect Prev; 3(2):471-485 1981

Having previously established gamma-glutamyltransferase (GGT) as a marker of experimental carcinogenesis in rat liver, we investigated whether human tumors differ from their tissue or origin by showing a higher activity or different localization of this enzyme histochemically. We found such differences in each of the human carcinomas we examined. The presence of GGT activity in carcinomas arising in organs normally containing little (tongue) or no GGT activity (larynx, urinary bladder, and esophagus) clearly distinguished cancerous from normal epithelium. In the breast, colon and prostate, GGT activity was normally present in a defined anatomical distribution bordering luminal surfaces. Carcinomas arising from these tissues showed a loss of the normal pattern of activity and contained cells with almost homogeneous GGT activity in the cytoplasm. Such differences clearly distinguished carcinomatous from normal epithelium in these organs. The increased GGT activity observed in all nine carcinomas arising from seven different organs suggests that GGT may be a common marker of human epithelial tumors and staining for GGT may become a useful tool in the detection of human epithelial neoplasms. (Author abstract) (18 Refs)

54. FIBRONECTIN. IMMUNO-MORPHOLOGICAL STUDY OF ITS DISTRIBUTION IN HUMAN PATHOLOGY.

Birembaut P, Gaillard D, Adnet J-J, Dousset H, Kalis B, Poynard J-P, Leutenegger M, Labat-Robert J, Robert L
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Ann Pathol; 1(2):140-146 1981

Fibronectin (FN) is a major glycoprotein component of extra-cellular matrix. This glycoprotein seems to be involved in cell to cell interaction and in cell to extracellular matrix interaction. Its distribution has been studied in various pathological conditions by an indirect immunofluorescent technique using a rabbit anti-FN serum. In various carcinomas, there is a loss of FN normally present within basement membranes, related to tumoral infiltration. Of particular interest is the irregular labeling of basement membranes in intraductal mammary carcinomas and comedocarcinomas and in noninfiltrating bronchial carcinoma. This discontinuous pattern seems to correspond to a potential neoplastic invasive process. In mammary benign lesions there is an inconstant and variable pericellular labeling around epithelial cells. This pericellular FN is never found in severe dysplastic and malignant lesions of the breast. The disappearance of this pericellular and basement membrane FN could be of practical interest in the dete ction of early malignant lesions. In benign connective proliferations FN is localized principally on cellular surfaces and vascular basement membranes. In sarcomas, there is a loss of the regular pericellular labeling around sarcomatous cells. These observations correlate well with cellular culture findings. Loss of pericellular FN seems to be related to malignant transformation. Detection of FN would be of diagnostic value in pseudo-tumoral or inflammatory lesions of the soft tissues. In the normal skin, FN is present in papillary dermis principally. In the skin of diabetic patients, there is an increase of FN in the superficial dermis and a frequent labeling of epidermis basement membrane. Thickened vascular basement membranes are also labeled by anti-FN serum. FN seems to be involved in the diabetic microangiopathy. In sclerodermic processes, there are qualitative and quantitative modifications of the distribution of cutaneous FN. FN is abundant in the lower dermis, especially in active fibrotic lesions. In the renal parenchyma, FN is found in the mesangium of glomeruli and in vascular basement membranes of the interstitium. FN is a good marker of the mesangium in numerous proliferative glomerulonephritis. FN is also linked to fibrin in thrombotic microangiopathy, epithelial crescents and fibrinoid necrosis. FN is not found in amyloid deposits. (21 Refs) (In FRE)

55. STUDIES INTO CARCINO-EMBRYONIC ANTIGEN (CEA) AND ENZYME ACTIVITIES OF ALKALINE AND ACID PHOSPHATASE IN PATIENTS WITH FIBROCYSTIC BREAST DISEASE.

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Zentralbl Gynaekol; 103(10):564-568 1981

CEA as well as alkaline and acid phosphatase were measured in patients with fibrocystic breast disease. The values recorded from the punctured fluids were compared to those in peripheral blood. CEA concentrations in cyst fluid were elevated in patients with proliferative breast disease, whereas no correlations could be established between alkaline and acid phosphatase, on the one hand, and various histological forms of breast disease, on the other. (Author abstract) (20 Refs) (In GER)

56. MUSCULAR CHANGES IN CARCINOMAS OF THE BREAST.

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Zentralbl Allg Pathol; 125(2):128-138 1981

Fourteen samples of the Musculus pectoralis major from patients with early stages of breast cancer and three samples from patients with nonmalignant mammary diseases were stored in liquid nitrogen and investigated histologically, histochemically and histometrically. Main changes are lipomatosis, fiber necrosis, occasional perifascicular atrophy, metabolic changes (eg accumulation of lipids), and alterations of the activity of oxidative enzymes. Histometrically we found an atrophy of type 2 fibers. There may be relations between the degree of the muscle changes and the severity of the tumor disease. The paraneoplastic muscle disease is a 'concomitant myopathy' and may be regarded as a 'functional myopathy'. In its development we can differentiate a phase of compensation and a phase of decompensation. (Author abstract) (12 Refs)

57. ROLE OF MYOEPITHELIAL CELLS IN HISTOGENESIS OF BREAST CANCER.

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Arkh Patol; 43(7):13-20 1981

The results of histological, histochemical, and electron microscopic examination of the myoepithelial cells in normal breast tissue, hormonal dysplasia, and ductal carcinoma are reported. Proliferative mastopathy was characterized by the changes in the number and shape of myoepithelial cells, elevated activity of phosphohydrolases, and the presence of cytoplasmic pseudocysts containing collagen fibers. The specimens of invasive ductal carcinoma retained the features characteristic for myoepithelial cells (high activity of ATPase, presence of cytoplasmic fibrillae, and pinocytotic vesicles). (10 Refs) (In RUS)

58. GROWTH OF HUMAN MAMMARY EPITHELIAL CELLS ON COLLAGEN GEL SURFACES.

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Cancer Res; 41(10):4093-4100 1981

We have developed a method for sustained growth of human mammary epithelial cells in monolayer cultures. Epithelial organoids derived from solid breast tissues were grown on the surface of thin (approx 1 mm) collagen gel layers in an enriched growth medium supplemented with hormones, growth factors, fetal calf serum, and horse serum. To transfer the cultures, the collagen layers were dislodged and digested with collagenase. The monolayers of cells released into suspension were then dissociated into single cells using trypsin-ethylenediaminetetraacetate. Dissociated single cells were repleted with 75 to 95% efficiency onto collagen layers or tissue culture plastic surfaces. The dissociated cells could also be cryopreserved and reactivated with greater than 80% plating efficiency on collagen layers. Normal human mammary epithelial cells grown under these conditions progressed through 12 to 15 population doublings. The population-doubling times for normal and malignant mammary cells on collagen layers were 34 and 65 hr, respectively. After reaching confluence, cells in some cultures, derived from either normal or malignant tissues, penetrated the gel surface and grew into the collagen. Within the gels, the cells became organized into three-dimensional tubular structures. The use of collagen layers eliminates a major problem in growth of human mammary epithelial cells in culture, difficulty in efficient dissociation, and cell transfer from monolayers. (Author abstract) (11 Refs)

59. ISOLATION AND CHARACTERIZATION OF POLYPLOID NUCLEI OF R3230AC MAMMARY ADENOCARCINOMA AND COMPARISON WITH NORMAL MAMMARY NUCLEI.

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Cancer Res; 41(10):3907-3912 1981

The R3230AC mammary adenocarcinoma is biochemically similar to the normal lactating mammary gland in many ways, including the RNA/DNA ratio. However, the tumor differs from normal in important ways, which include having a DNA content 2 to 4x higher than the max value for normal mammary gland. This raises the question of whether the cells of the tumor all have more DNA than normal cells. In order to determine how tumor DNA is distributed and whether its transcriptional activity differs from normal, we have compared the ploidy and RNA polymerase activities of nuclei isolated from both sources. Nuclei were also examined for their content of Ca++-stimulated RNase activity, a marker of mammary differentiation. Sucrose density gradient centrifugation of tumor cell nuclei revealed three nuclear types, designated T1, T2, and T3, representing 25, 48, and 27% of total nuclei isolated. T1, T2, and T3 nuclei contained, respectively, 6.5, 12.3, and 19.0 pg DNA per nucleus, representing diploid, tetraploid, and hexaploid amounts of DNA. Nuclear RNA and protein increased in proportion to ploidy. By contrast, cell nuclei isolated from lactating mammary gland formed only two bands (M1 and M2), comprising 54 and 46%, respectively, of total nuclei isolated. Both M1 and M2 nuclei contained diploid amounts of DNA. Therefore, the higher DNA content in the tumor is attributable, at least in part, to the presence of polyploid nuclei in the majority of tumor cells. The combined activity of DNA-dependent RNA polymerases I, II, and III per nucleus was the same in T1, T2, and T3; M1 and M2 also had activities similar to each other but much lower than the tumor types. Activity attributable to polymerase I (resistant to 200 ug alpha-amanitin per ml), polymerase II (inhibited by 0.06 ug alpha-amanitin per ml), and polymerase III (inhibited by 200 ug alpha-amanitin per ml) was about 35, 50, and 15%, respectively, for each class of tumor nuclei. The corresponding values for M bands were about 44, 34, and 22%. These results suggest that tumor cells synthesize more heterogeneous RNA than do mammary cells of lactating rats, but the latter synthesize more ribosomal RNA. Activity of mammary-specific Ca++-stimulated RNase increased slightly per nucleus as the ploidy of tumor nuclei increased, but in every T group the activity was less tha n one-half of that of M1 or M2 nuclei. Thus, despite differences in ploidy, all tumor nuclear classes show a lesser degree of differentiation than nuclei from the lactating gland, with respect to their capacity for synthesis of ribosomal RNA compared to messenger RNA and their expression of Ca++-stimulated RNase. (Author abstract) (31 Refs)

60. KINETICS OF CELL PROLIFERATION IN SPONTANEOUS MAMMARY TUMOUR IN MICE OF LINE C57BL.

Botev BA, Topashka-Ancheva MN, Karaivanova MH
Oncology Res. Inst., Sofia Medical Acad., Sofia, Bulgaria
Dokl Bolg Akad Nauk; 34(4):561-564 1981

The results of an autoradiographic study of a spontaneous, transplantable C57BL mouse mammary tumor are reported. The tumor cell population was characterized by a short cell cycle and a relatively low cell loss, which permitted the progressive growth of the tumors in syngeneic recipients. (11 Refs)

61. TUMOR-SPECIFIC POLYADENYLATED RNA'S FROM 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS REVEALED THROUGH HYBRIDIZATION WITH FRACTIONATED SINGLE-COPY DNA.

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Cancer Res; 41(10):3827-3834 1981

Polyadenylated (poly(A)+) and nonpolyadenylated (poly(A)-) RNA fractions from primary, hormone-dependent, 7,12-dimethylbenz(a)anthracene-induced mammary tumors and normal rat mammary tissue were analyzed by molecular hybridization to determine if there is a unique class of 'tissue-specific' RNA sequences. Single-copy [3H]DNA was fractionated into probes which were either depleted of midpregnant RNA sequences or complementary to these same sequences. When these probes were annealed to homologous and heterologous poly(A)+ RNA's, distinct sets of single-copy sequences were found in the two poly(A)+ RNA populations. The complexity of the 'tumor-specific' sequences was about 6.7 x 10(7) nucleotides (assuming asymmetrical transcription). Hybridization of the poly(A)- RNA fractions isolated from the 7,12-dimethylbenz(a)anthracene-induced tumors and the normal mammary gland to poly(A)- complementary DNA's revealed that both tissues appear to contain a class of poly(A)- RNA sequences which were distinct from the set of poly(A)+ RNA's. Both poly(A)- RNA fractions saturated at 3% when hybridized to single-copy [3H]DNA. However, approx 15 to 25% (minimum estimate) of the complexity of the poly(A)- RNA was contributed by contaminating poly(A)+ RNA sequences. Therefore, the actual complexity of the poly(A)- RNA fractions was 2.0 to 2.5% of the single-copy hybrid genome. Mixtures of these two RNA fractions also gave a saturation value of 3.0% when annealed to single-copy [3H]DNA. This indicated that most of the poly(A)- RNA's were similar in the neoplastic and normal mammary tissues. Although the majority of the infrequent R NA species are held in common between the two tissues, there is a distinct set of high-complexity poly(A)+ RNA sequences, presumably of nuclear origin, which is unique to the 7,12-dimethylbenz(a)anthracene-induced tumors. Whether these RNA's are processed and became functional messenger RNA's is not known. Presumably, they play a role in regulating the frequencies of the tissue-specific abundant and moderately abundant messenger RNA's and therefore provide one mechanism by which the concentration of specific proteins and ultimately the expression of the transformed phenotype may be regulated. (Author abstract) (40 Refs)

62. CYTOGENESIS OF MURINE MAMMARY TUMORS IN BALB/CFC3H AND BALB/CFRIII STRAINS.

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Histochemistry; 72(1):49-53 1981

The C3H and RIII variants of the murine mammary tumor virus show different biological behavior and morphology in BALB/cf mice that carry these strains, but the mechanism of these differences is not known. The involvement of two different mammary cell types must be considered: epithelial and myoepithelial cells. Four tumors from each of the two strains (BALB/cfC3H and BALB/cfRIII) were processed to test the ATPase activity of their plasma membranes: tumor fragments were fixed, washed, embedded, sectioned, and incubated in one of two media, the first capable of demonstrating a Mg++-dependent ATPase (which is present on the plasma membranes of both epithelial and myoepithelial cells) and the second capable of demonstrating a Na+/K+-dependent ATPase (which is present only on the plasma membrane of myoepithelial cells). Electron microscopic examination, of the specimens showed viral particles of both A and B types present but distributed differently in tumors of the two strains. The histochemical results were (1) both types of tumor fragment showed Mg++-dependent but not Na+/K+-dependent ATPase activity on the cells' plasma membranes, (2) no positive reaction was seen in tissue incubated without ATP, and (3) no differences were seen in positive cases between tissue stained with uranyl acetate alone and those stained with uranyl acetate and lead citrate. These results suggest that myoepithelial cells do not participate in the growth of the tumors studied here. (11 Refs)

63. X-RAY MICROANALYSIS OF ELECTROLYTE CONTENT OF NORMAL, PRENEOPLASTIC, AND NEOPLASTIC MOUSE MAMMARY TISSUE.

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Cancer Res; 41(10):3877-3880 1981

Intracellular sodium, chlorine, and potassium concentrations (mmol/kg dry wt) were determined by electron probe x-ray microanalysis of an individual epithelial cells in freeze-dried 2-um sections of mouse mammary tissue which were cut at-30 C. A model system was utilized in order to compare elemental content of cells from normal pregnant mammary tissue and preneoplastic and neoplastic mammary tissues from female BALB/cCrlMed mice. Animals were killed by cervical dislocation, and tissue was rapidly frozen in liquid propane. Normal mammary glands were obtained from primiparous mice at 16 or 17 days of gestation. Tissue from the hyperplastic alveolar nodule line D1 was removed from donor mice 12 to 16 wk after transplantation into the cleared mammary fat pad. All mammary adenocarcinomas, D1T, were primary tumors which developed in mice with transplants of nodule line D1. Data were collected from five animals (10 cells/animal) in each of the three groups. It was found that the electrolyte content of cells of preneoplastic tissue was the same as that of the normal mammary tissue but was significantly elevated in neoplastic tissue (162, 130, and 48% increases for sodium, chlorine, and potassium, respectively). Thus, an increase in electrolyte content seems to be associated with the transformation to a neoplastic state and not associated with conversion to the preneoplastic state. (Author abstract) (30 Refs)

64. ON SUPPRESSION OF TUMORIGENICITY IN HYBRID AND CYBRID MOUSE CELLS.

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Somatic Cell Genet; 7(4):457-471 1981

An attempt was made to find evidence for a cytoplasmic influence on the suppression of tumorigenicity in mouse cells. Cybrids (THBU cybrids) were constructed between whole tumorigenic mouse mammary cells (BALB/c, cell line C2B2 from line MT29240) and enucleated nontumorigenic cells (BALB/c, cell line THOC from clone A31) bearing complementary (nuclear and cytoplasmic) genetic markers. The cybrids were examined for some parameters of in vitro transformation and for tumorigenic capacity and compared to the parental cells. No genetic complementation occurred between the two in vitro transformed parents (THO from clone A31 and C2B2) that could restore the untransformed phenotype in the hybrid cells. In contrast, a strong suppression of tumorigenicity was observed in these hybrids. The analysis of THBU cybrids suggested that the capacity of C2B2 cells to form tumors in vivo can be significantly reduced following fusion with cytoplasts of nontumorigenic cells. This reduction was insufficiently stable or generalized to be observed when mixtures of cybrid colonies were assayed but, for most of the single cybrid clones analyzed, it was clearly expressed in terms of lower take incidence and/or more extended latent periods. (45 Refs)

65. BASAL LAMINA FORMATION BY NORMAL AND TRANSFORMED MOUSE MAMMARY EPITHELIAL CELLS DUPLICATED IN VITRO.

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JNCI; 67(3):719-728 1981

Cells from low-passage (LP) cultures of a mouse mammary epithelial line (NMuMG cells) form a basal lamina when they are cultured on a Type I collagen gel substratum. A high-passage (HP) strain of this line maintained the morphologic, serologic, and karyologic properties of the LP cells. For the determination of whether transformation of the NMuMG cells might lead to defects in the basal lamina, cells from LP cultures were compared in vivo and in vitro with cells of HP cultures for tumorigenicity, growth characteristics, and ability to form a lamina. The LP NMuMG cells had a typical epithelial morphology and showed no cytologic evidence of cancer. They formed an ultrastructurally normal continuous basal lamina in vivo when they were injected into athymic nude mice. In contrast, the HP cells were pleomorphic and highly invasive when injected into nude mice where they showed frequent and large basal lamina defects. These cells also accumulated only traces of lamina-like materials when cultured on a collagen gel, indicating that neoplastic transformation had markedly reduced the ability of NMuMG cells to form a basal lamina both in vivo and in vitro. Because the collagen gel culture system duplicated the in vivo situation with regard to basal lamina integrity, the basis for this lack of in vitro basal lamina formation may be physiologically relevant for the mechanism of malignant invasion. (Author abstract) (33 Refs)

66. NATURALLY ARISING TUMORS OF THE INBRED WAB/NOT RAT STRAIN. I. CLASSIFICATION, AGE AND SEX DISTRIBUTION, AND TRANSPLANTATION BEHAVIOR.

Middle JG, Robinson G, Embleton MJ
Dept. Chemical Pathology, Royal Liverpool Hosp., Prescot St., Liverpool, L7 8XP, England

JNCI; 67(3):629-636 1981

During a 3-yr period, 97 naturally arising tumors were collected from an inbred colony of WAB/Not rats. These tumors were largely confined to the breeding groups of approximately 5,300 female and 2,700 male rats retained up to 2 yr of age. The tumors included 39 nephroblastomas and 41 mammary tumors (24 of which were histologically benign); the remaining tumors were mainly connective tissue sarcomas and skin tumors with 1 lymphoma and 2 gastrointestinal lesions. With the exception of the incidence of mammary tumors, males and females had similar tumor incidence, although nephroblastomas in female rats had a marked preference for growth in the left kidney. Most tumors occurred in the 1st yr of life, especially the histologically malignant mammary tumors and the nephroblastomas. Of the tumors investigated, 31 were transplantable. Poor correlation between histologic malignancy and transplantation was seen with the mammary tumors. Only 50% of the nephroblastomas were transplantable. Although most transplanted tumors retained histologic characteristics of the primary tumor, one mammary tumor, one gastrointestinal tumor, and one nephroblastoma deviated from this general finding. In the case of this nephroblastoma, separate transplant lines from opposite poles of the primary tumor also showed differences in histology. (Author abstract) (26 Refs)

67. MAMMARY DUCT ECTASIA.

Chinoy R, Talvalkar GV
Tata Memorial Hosp., Dr E . Borges Marg, Parel, Bombay 400 012, India
Indian J Cancer; 18(2):128-133 1981

Among 2,859 non-neoplastic lesions of the breast diagnosed between 1955 and 1978, there were 45 cases of duct ectasia in women aged 26-65 yr (av age 41 yr). Symptoms included breast lump in 41 patients, breast lump with pain in 6, bloody nipple discharge in 2, milky nipple discharge in 3, fever in 3, and nipple retraction in 4. Preoperative diagnosis was carcinoma in 23 cases, chronic mastitis in 6, and inflammatory mastitis with or without abscess in 7. Tubercular lesions were suspected in four cases, fibroadenoma in one, and papilloma in four. Only one diagnosis of carcinoma, duct ectasia was made. Histologic criteria useful for diagnosis included distended ducts filled with fatty debris and crystalline bodies, atrophic duct epithelium, periductal fibrosis, and granulomatous inflammation. Seven patients underwent mastectomies. No patient returned for treatment of a malignancy. Emphasis is placed on the uncanny clinical resemblance of mammary duct ectasia to malignancy. Useful features for the diagnosis of mammary ectasia in all phases of development are presented. (8 Refs)

68. ROLE OF BIOGENIC AMINES AND THEIR RELATED ENZYMES IN CANCER CASES.

Prasad GC, Chaurasiya J, Mohanty S
Inst. Medical Sciences, Banaras Hindu Univ., Varanasi 5, India
Indian J Cancer; 18(2):103-107 1981

Serotonin, gamma-aminobutyric acid (GABA), glutamate, monoamine oxidase (MAO), and histaminase (HIS) were estimated in the plasma of 24 cancer patients and were compared to values from 36 patients with brain tumors. There were 10 patients with breast cancer, 5 with stomach cancer, 3 with thyroid cancer, 3 males with hypernephroma, and 1 male each with leukemia, lymphosarcoma, and seminoma of the testes. Serotonin was significantly higher in most of the patients compared with normal controls, with max increases in cases of breast cancer, stomach cancer, and myeloid leukemia. Significant decreases in MAO values were noted in most of the cancer patients. Brain tumors demonstrated a significant increase in MAO levels. Plasma HIS was elevated in all cancer cases, with the most significant increase in the case of seminoma of the testes. GABA was below normal levels in all cancer cases except those of the brain, stomach or seminoma testes. Glutamate was significantly increased in cancer patients compared with normal controls. The use of these biogenic amines and their related enzymes for the diagnosis and progress and therapeutic decisions of cancer management is suggested. (20 Refs)

69. BIOLOGICAL BEHAVIOR OF HUMAN MALIGNANT TUMORS GROWN IN THE NUDE MOUSE.

Kyriazis AP, Kyriazis AA, McCombs WB, Kereiakes JA
Dept. Pathology, Univ. Cincinnati Medical Center, MSB, R-1253, Cincinnati, OH, 45267
Cancer Res; 41(10):3995-4000 1981

The biological behavior of a number of nude mouse-grown human epithelial tumors of different histogenetic background were studied. They included three transitional cell carcinomas and a mucin-producing carcinoma of the urinary bladder, two pancreatic adenocarcinomas, a colon adenocarcinoma, a breast ductal carcinoma, and an epidermoid carcinoma. Microinvasion was a constant finding in all tumors examined. All but one of the tumors studied showed macroinvasion and metastases. Tumors transplanted sc in the anterior aspect of the lateral thoracic wall metastasized primarily to the regional and mediastinal lymph nodes. In certain cases, systemic metastases were observed affecting the submaxillary, contralateral axillary, and inguinal lymph nodes. Lung metastases occurred through the lymphatic and hematogenous routes. It is concluded that the nude mouse-grown human tumors investigated in the present study show overt malignant behavior recapitulating the biological characteristics of the tumor of origin. (Author abstract) (27 Refs)

REVIEWS AND OTHER RELATED STUDIES

70. PRENEOPLASTIC LESIONS OF THE MAMMARY GLAND. (ONCOLOGY OVERVIEW)

International Cancer Research Data Bank
ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Preneoplastic Lesions of the Mammary Gland (Oncology Overview) Medina, D, ed This Title is Available Through National Technical Information Service, Springfield, VA, us NTISUB/PB81-923002; OB-81/02:134pp. 1981

Oncology Overviews are a service of the International Cancer Research Data Bank (ICRDB) Program of the National Cancer Institute. They are retrospective bibliographies containing 100-500 selected abstracts of published research on topics of high interest to cancer investigators. The scope of this Oncology Overview emphasizes the basic biological aspects of preneoplastic and pseudoneoplastic lesions of human, rodent, and canine mammary glands in vivo and in vitro. Induction and modulation of mammary preneoplasias by carcinogens, hormones and other agents, as well as hormonal responsiveness, immunologic aspects, cytogenetics, and angiogenesis studies are presented. Also of interest are metabolic, enzymatic, and histochemical evaluations of preneoplastic breast lesions. In studies of mammary preneoplasias in humans, ultrastructural and histopathological characteristics, radiologic evaluation, cytology of aspiration s and secretions, and cytomorphometry are included. Risk estimates of malignant potential of these breast lesions are also considered. The Overview excludes studies purely concerned with the treatment and/or management of patients with breast preneoplasias.

71. PATHOBIOLOGY OF BREAST CANCER: HYPOTHESIS OF BIOLOGICAL PREDETERMINATION AND LONG-TERM SURVIVAL.

Vorherr H
Dept. Obstetrics-Gynecology, Univ. New Mexico Sch. Medicine, 915 Stanford Drive, N.E., Albuquerque, NM, 87131
Klin Wochenschr; 59(15):819-829 1981

The pathobiology of breast cancer is complex: clinically 'early' breast cancer may be tumor-biologically 'late' progressing rapidly toward death. Accordingly, it has been suggested that two different breast cancer populations (slow tumor growth and long survival - fast tumor growth and short survival) exist, which cannot be identified by pathohistological criteria. However, these 'populations' are most likely either patients with localized disease and occult metastases (long survival) or with diagnosable regional and occult or overt systemic spread (short survival). Since even small tumors (0.1 to 0.3 cm in diameter) can spread systemically, in most patients breast cancer upon clinical diagnosis may be considered an inevitably lethal disease. Present treatment modalities can only improve the quality of life and delay death, even though the overall long-term survival rates of breast cancer are better or at least equal to those of other cancers. However, with other cancers it is decided within the first 5 yr which patients are cured because the survival rates for 5, 10, 15, and 20 yr are similar. In contrast, survival rates of patients with breast cancer steadily decline and there is no point in time when patients can feel really safe; this is indicative of a peculiar tumor pathobiology of this disease, the nature of which remains to be investigated. Progress in the fight against breast cancer is only possible by application of sensitive physical, reliable immunological, and specific biochemical methods for early diagnosis and development of efficient therapeutic modalities for inhibition of growth or complete eradication of metastasized cancer cells. (Author abstract) (74 Refs)

72. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.

Kochergina NI, Kosova IP
Res. Lab. Experimental Immunobiology, Moscow, USSR
Usp Sovrem Biol; 91(3):409-418 1981

Literature data on tumor factors that can stimulate or inhibit proliferation of normal or neoplastic cells are reviewed. Factors isolated from murine sarcoma 180, spontaneous and explanted murine mammary gland carcinomas, tissue-specific inhibitors of cell divisions (chalones), and polysomal RNA from Rous sarcoma cells were found to regulate the neoplastic growth and to affect tumor transplantability. Tumor factors were shown to inhibit the antibody formation. The sera of cancer patients was shown to contain factors that inhibited lymphocyte cytotoxicity. In response to stimulation with tumor antigens, T lymphocytes formed the clone of killer cells. The degree of lymphocyte transformation depended upon the ratio of lymphocytes and tumor antigen. Tumor factors were found to inhibit not only the antitumor but also the transplacental immunity. Stimulation of tumor antigenicity can stimulate the immune system of tumor-bearing organism and thus can have an immunotherapeutic effect. (108 Refs) (In RUS)

73. ENDOGENOUS CARCINOGENS.

Hill MJ
Bacterial Metabolism Res. Lab., Central Public Health Lab., London, England
Practitioner; 225(1356):803-804,807-809 1981

Estradiol is a potential endogenous carcinogen. Consuming a high fat/high energy diet, by increasing circulating estrogen levels and estrogen receptor activity, may increase the risk of carcinogenesis in estrogen-dependent tissues (breast, endometrium, possibly ovary). The role of of cholesterol in carcinogenesis is not yet clear. The author's studies showed no relationship between fecal cholesterol levels and the risk of intestinal cancer in case-control studies. Some of the numerous urinary metabolites of tryptophan seem to be related to non-industrial bladder cancer. Intestinal bacteria can derive carcinogenic substances (ethionine, phenol, p-cresol, N-nitroso compounds, bile acid metabolites, etc) from dietary components and convert exogenous chemicals (eg, polycyclic aromatic hydrocarbons) to proximate carcinogens. It is relatively easy to determine which carcinogens might be produced under ideal conditions, but there is limited information on which carcinogens are actually produced in vivo, and very little information regarding their importance. (27 Refs)

74. TUMOR MARKERS.

Statland BE
No affiliation given
Diagn Med; 4(4):21-25,28,29,32,33,36,38 1981

Eleven groups of clinical chemistry analytes which have been used successfully in evaluating patients with cancer are reviewed. Oncofetal antigens used include alpha-fetoprotein, tissue polypeptide antigen, Tennessee antigen, fetal sulfoglycoprotein, pancreatic oncofetal antigen, and mammary tumor-associated glycoprotein. Pregnancy-associated proteins of diagnostic utility are human chorionic gonadotropin, pregnancy-specific glycoprotein, and pregnancy-associated alpha-Z-glycoprotein. Other proteins that are valuable as tumor markers include certain glycoproteins (eg those associated with sialic acid), acute phase reactants (eg haptoglobin, orosomucoid, and alpha-1-antitrypsin), ferritin, and casein. Enzymes synthesized by tumor cells include certain glycosyltransferases, placenta-like alkaline phosphatase, and prostatic acid phosphatase. Because bone and liver are frequent sites of metastatic carcinoma, enzymes derived from liver tissue and from bone tissue can be monitored. Osteolytic metastases (important in patients with breast cancer) are associated with the breakdown of collagen in bone; the relative urinary excretion of amino acid derivatives unique to collagen (vis hydroxyproline:creatinine ratio) is of diagnostic interest. Polyamines, nucleosides, cellular markers (eg T-cell and B-cell markers), and steroid receptors are also used for classification of malignancy. (42 Refs)

75. PROTECTIVE EFFECT OF ORAL CONTRACEPTIVES AGAINST CANCER OF THE REPRODUCTIVE ORGANS.

Johansson ED, Svanstrom L
Kvinnokliniken, Akademiska sjukhuset, Uppsala, Sweden
Lakartidningen; 78(28/29):2591-2592 1981

Studies on the protective effect of oral contraceptives, especially combined contraceptives, against cancer in the reproductive organs are reviewed. The combined oral contraceptives are more or less gestagen-dominated. They can therefore be expected to reduce the frequency of estrogen-dependent tumors. There is no clear evidence of a reduced incidence of breast cancer among women using such combined oral contraceptives: most studies show no change in the frequency of breast cancer, but one study showed reduced breast cancer risk in the age group 31-40 yr, and increased breast cancer risk in women who continued taking oral contraceptives beyond the age of 45 yr. Some studies showed a lower growth and later metastasized breast cancer in women who had used oral contraceptives compared with women who had not used contraceptives. The epidemiological studies show a marked reduction of the frequency of ovarian and endometrial cancer in women who had used oral contraceptives to half to one third of the frequency in women who had not used oral contraceptives. (12 Refs) (In SWE)

76. SOME RISK FACTORS OF BREAST CANCER.

Scolozzi R, Salmi R, Coccafogli A, Dell'Acqua G
Istituto di Clinical Medica Generale e Terapia Medica, Universita, Ferrara, Italy
Recenti Prog Med; 70(5):463-486 1981

Studies on the risk factors of breast cancer are reviewed. High stature, overweight (obesity), early menarche, hyperestrogenic, reduced fertility, advanced age at first childbirth, short overall duration of lactation, high-caloric, high-fat diet, long-term use of oral contraceptives, especially before the first pregnancy, late menopause, and exposure to ionizing radiation, especially during and shortly after puberty are generally recognized risk factors along with family history of breast cancer. The long-term use of hair dyes, especially of permanent ones, is also considered a risk factor for breast cancer along with other cancers. (134 Refs) (In ITA)

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CHEMICAL CARCINOGENESIS

1. TOXICOLOGICAL ASPECTS OF POLYCYCLIC AROMATIC HYDROCARBONS (PAH).
De Fernicola NA, De Azevedo FA
Divisao de Toxicologia e Ecotoxicologia, Diretoria de Tecnologia e Desenvolvimento, Sao Paulo, Brazil
Rev Bras Saude Ocup; 33(9):62-68 1981
In POR

2. EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS: SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
International Agency for Research on Cancer
International Agency for Res. on Cancer, Lyon, France
IARC Monogr Eval Carcinog Risk Chem Hum; 26:1-411 1981

3. STUDIES ON THE ROLE OF ORAL CONTRACEPTIVE USE IN THE ETIOLOGY OF BENIGN AND MALIGNANT LIVER TUMORS.
Mettlin C, Natarajan N
Cancer Control and Epidemiology, Rosewell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Surg Oncol; 18(1):73-85 1981

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4. EXPERIMENTAL RADIATION CARCINOGENESIS: WHAT HAVE WE LEARNED?
Fry RJ
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5. INFLUENCE OF NONCARCINOGENIC SECONDARY FACTORS ON RADIATION CARCINOGENESIS.
Little JB
Lab. Radiobiology, Harvard Univ., Sch. Public Health, Boston, MA, 02115
Radiat Res; 87(2):240-250 1981

6. MEDICAL IRRADIATION IN JAPAN - STOCHASTIC RISK ESTIMATION AND ITS REDUCTION.
Hashizume T
Div. Physics, National Inst. Radiological Sciences, 9-1 Anagawa 4-Chome, Chiba Shi 260, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(5):445-474 1981
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7. RADIOACTIVITY IN DRINKING WATER.
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Office of Drinking Water, Environmental Protection Agency, Washington, DC
Radioactivity in Drinking Water. Available from National Technical Information Service, Springfield, VA, as PB81-192833:, 79 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

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NCIC Epidemiology Unit, Univ. Toronto, McMurrich Building, Toronto, Ontario M5S 1A8, Canada
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10. PANCREATIC CANCER.
Cohn I, Hastings PR
Dept. Surgery, Louisiana State Univ., 1542 Tulane Ave., New Orleans, LA, 70112
UICC Tech Rep Ser. Vol. 57, Issue 12, 142 pp., 1981.

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Marks PA
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Blood; 58(3):415-419 1981

12. ETIOLOGY, ROLE AND DETECTION OF CHROMOSOMAL ABERRATIONS IN MAN.
Fabricant JD, Legator MS
Dept. Preventive Medicine, Div. Environmental Toxicology, Univ. Texas Medical Branch, Galveston, TX, 77550
JOM; 23(9):617-625 1981

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13. INDUSTRIAL CARCINOGENESIS.
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16. ASBESTOS, AN ENVIRONMENTAL POLLUTANT.
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17. REVIEW OF UICC PROGRAM ON SMOKING AND LUNG CANCER.
Gray N
Smoking and Cancer Program, UICC, 3 rue du Conseil General, 1205 Geneva, Switzerland
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18. EXPERIMENTAL APPROACHES TOWARDS THE BIOCHEMICAL ANALYSIS OF CHEMICAL CARCINOGENESIS.
Laishes BA
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Magrath IT
Pediatric Oncology Branch, Div. Cancer Treatment, NCI, NIH, Public Health Service, United States Dept. Health and Human Services, Bethesda, MD, 20205
JNCI; 67(3):501-514 1981

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22. FACTORS STIMULATING AND INHIBITING TUMOR GROWTH IN CARCINOGENESIS.
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Res. Lab. Experimental Immunobiology, Moscow, USSR
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24. BURKITT'S LYMPHOMA.
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25. REVIEW ARTICLE. REGULATION OF EXPRESSION OF THE INTEGRATED RETROVIRUS GENOME.
Weinberg RA, Steffen DL
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J Gen Virol; 54(part1):1-8 1981

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26. THE DEVELOPMENT AND VALIDATION OF MUTAGENICITY SCREENING TESTS.
Durkin PR, Santodonato J
Center for Chemical Hazard Assessment, Syracuse Res. Corporation, Merill Lane, Syracuse, NY, 13210
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27. SHORT-TERM TEST SYSTEMS FOR POTENTIAL MUTAGENS AND CARCINOGENS: I. MICROBIAL TESTS (ONCOLOGY OVERVIEW).
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ICRDB Program Office, NCI, Westwood Building, Room 10A18, Bethesda, MD, 20205
Short-Term Test Systems for Potential Mutagens and Carcinogens: I Microbial Tests (Oncology Overview) Simmon, V F; Peirce, V; eds This Title is Available Through National Technical Information Service, Springfield, VA, as NTISUB/PB81-922903:; OK-81/03:124pp. 1981

28. ANIMAL MODELS OF INTRA-ORAL CHEMICAL CARCINOGENESIS: A REVIEW.
Eveson JW
Dept. Oral Medicine and Pathology, Guy's Hosp., London SE1 9RT, England
J Oral Pathol; 10(3):129-146 1981

29. THE CHROMOSOMES IN HEMATOLOGY.
Berger R
Laboratoire de Cytogenetique, Institut de Recherches sur les Leucemies et les Maladies du Sang, UER d'Hematologie, Hopital Sant-Louis, 2 place du Dr. Fournier, 75475 Paris Cedex 10, France
Cancer Genet Cytogenet; 4(1):69-88 1981

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ORGAN SITE CARCINOGENESIS

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service • National Institutes of Health • National Cancer Institute

HE 20. 3173/2:

PREVALENCE OF BREAST CANCER IN HUMAN POPULATIONS

1. CANCER INCIDENCE IN QUEBEC (1971-1975) AND CARTOGRAPHY.

Thouez JP, Beauchamps Y, Dubois A, Simard A
Departement de geographie, Universite de Montreal, C.P. 6128, Montreal, Quebec, Canada
Union Med Can; 110(9):798-802 1981

A method is described for the geographic mapping of regional variations in the incidence of certain types of cancer observed in the province of Quebec between 1971 and 1975. Age-adjusted rates of cancer show a higher incidence of cancer in males. Cancer mortality rates in Quebec province have been found to be greater than those observed for Canada as a whole. The existence of artifical regional variations resulting from methods of data collection and analysis has been proposed. Geographic maps of standardized incidence ratios for breast, intestine, prostate, cervix, rectosigmoid, trachea, bronchi, and lungs cancers in the 74 federal counties of Quebec is presented. These representations indicated that cancers of trachea, bronchi, and lungs occur at similar rates in urban and rural areas. Breast cancer occurs more often in urban areas as compared with cervix cancer. Cancers of the rectum and intestine show similar geographical distributions. Prostate cancer shows many major geographic concentrations. (14 Refs) (In FRE)

2. DESCRIPTIVE EPIDEMIOLOGY OF BREAST CANCER IN THE CITY AND PROVINCE OF TORINO.

Colombo A, Rendine S, Zanetti R
Cattedra di Epidemiologia dei Tumori, Via Santena 7, 10126 Torino, Italia
Tumori; 67(4):273-278 1981

Between 1950-54 and 1970-74 the mortality rates from breast cancer showed a 35% increase in Italy. In the city of Torino, an increase occurred between 1950-54 and 1960-64 but not in the following 10-yr period. These trends were confirmed by the analysis of rates by cohorts of birth. In the province of Torino between 1960-64 and 1970-74 the increase in breast cancer death rates was far lower than in the other provinces of Piedmont. It is suggested that the peculiar patterns in the city and in the province of Torino reflect qualitative changes of lifestyle brought about by the conspicuous migration from southern Italy during the sixties. (Author abstract) (14 Refs)

3. ATLAS OF CANCER MORTALITY IN THE PEOPLE'S REPUBLIC OF CHINA. AN AID FOR CANCER CONTROL AND RESEARCH.

Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD
Dept. Cancer Epidemiology, Cancer Inst. Chinese Acad. Medical Sciences, 2, Yabao Lu, Chaoyang, Qu, Beijing, People's Republic of China
Int J Epidemiol; 10(2):127-133 1981

A set of maps which display the patterns of cancer mortality in China has been prepared and published by the China Map Press. The 200 page atlas was edited by the National Cancer Control Office of the Ministry of Health and the Nanjing Institute of Geography of the Chinese Academy of Sciences on the basis of a nation-wide cancer mortality survey. The Cancer Institute of the Chinese Academy of Medical Sciences with related Colleges, Universities and Institutes provided the data and took part in the preparation of the atlas, which is published both in Chinese and English. Fifty eight maps and several dozen charts depict, in seven colors, the mortality distribution in the 2,392 counties and county-level administrative units of nine types of cancer common in China - stomach, esophagus, liver, cervix, lung, colon and rectum, breast, nasopharynx, and leukemia as well as five less common cancers - brain tumors, malignant lymphoma, cancer of the bladder, of the penis, and choriocarcinoma. The Atlas of Cancer Mortality will be an important new aid for cancer control and research in the People's Republic of China. (Author abstract) (10 Refs)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

4. CHARACTERISTICS OF FAMILIAL BREAST CANCER IN SWEDEN: ABSENCE OF RELATION TO AGE AND UNILATERAL VERSUS BILATERAL DISEASE.

Adami HO, Hansen J, Jung B, Rimsten A
Dept. Surgery, Univ. Hosp., S-750 14 Uppsala, Sweden
Cancer; 48(7):1688-1695 1981

A case-control study was conducted to examine the hypothesis that familiality in breast cancer is a heterogeneous entity. A study of 1,330 women, recently diagnosed as having breast cancer, compared, by paired sampling from a population register, the same number of age-matched women without a history of breast cancer. Data obtained by mailed questionnaires revealed a familial history in a first-degree relative in 149 patients and 90 controls (standardized relative risk/SRR/ = 1.7). The figures for second degree relatives were 115 and 81, respectively (SRR = 1.5). A detailed analysis of age at diagnosis and the occurrence of bilateral disease in the probands and their first-degree relatives with breast cancer failed to confirm any significant trend towards characterization of familial cases by early occurring or bilateral disease. The SRR for breast cancer in a first-degree relative was 1.7 for women with unilateral disease and 2.2 for those with bilateral. A slightly higher but nonsignificant relative risk was found for women diagnosed before (SRR = 2.4) than after (SRR = 1.7) 50 yr of age. Familial cases did not run a higher risk of developing bilateral disease than nonfamilial -6 and 5%, respectively. No patient or control reported premenopausal and bilateral disease in her mother, whereas three patients and five controls reported these characteristics in one of their sisters. The correlation between age at diagnosis in familial patients and their mothers or sisters with breast cancer was low -0.38 and 0.29, respectively/ - and there was no correlation with respect to the occurrence of bilateral disease within the families. (Author abstract) (23 Refs)

5. PROLONGED SURVIVAL AS A COMPONENT OF HEREDITARY BREAST AND NONPOLYPOSIS COLON CANCER.

Lynch HT, Albano W, Recerbaren J, Lynch PM, Lynch JF, Elston R
Creighton Univ., 2500 California St., Omaha, NE, 68178
Med Hypotheses; 7(9):1201-1209 1981

The survival in hereditary breast and colorectal cancers are compared with corresponding population norms. These findings form the basis for discussion of an hypothesis with mechanisms of host control. Survival was tabulated retrospectively for 106 patients with hereditary breast cancer (20 unrelated families) and 117 patients with hereditary carcinoma of the colon (18 unrelated families, none exhibiting multiple polyposis of the colon). Comparison data were obtained from the long-term audits of the American College of Surgeons (ACS) Tumor Registry for Breast and Colon Cancer. No appreciable differences in presenting stage were observed between the hereditary patients and those of the ACS Registry. The av age of diagnosis of the 106 hereditary breast cancer patients was 49, with 35.2% under age 45. The av age at diagnosis in the ACS Breast Tumor Registry Study was 57 yr with only 15.9% of the patients diagnosed under age 45. Of 106 breast cancer patients, 85 were followed for at least 5 yr with 57/85 remaining disease-free. Of the 73 patients surviving 10 yr or more, 39 were disease-free. The 5-yr disease-free survival in the ACS group was only 45.2%. The mean age at diagnosis of the 117 patients with hereditary nonpolyposis colon cancer was 46 yr, with 36.5% less than 40 yr old at the time of diagnosis. Only 6% of the patients with colon cancer in the ACS Registry were under age 40. The overall 5-yr disease-free survivorship was 52% in the hereditary colon cancer population, significantly better than the 35.3% rate in the ACS population. Improved survival in this limited number hereditary breast and colon cancer patients suggested that host factors may play a major role in not only etiology, but natural history of cancer as well. Clinical observation and cancer survival, spontaneous regression of cancer and cancer resistance, and an hypothesis of survival benefit and implications of this hypothesis for therapeutic trials are discussed. (28 Refs)

6. CANCER AND STRESS: COUNSELLING THE CANCER PATIENT.

Simonton OC, Matthews-Simonton S
Cancer Counseling and Res. Center, Suite 710, 1300 Summit, Forth Worth, TX, 76102
Med J Aust; 1(13):679,682-683 1981

In addition to the commonly accepted etiological agents of cancer, such as chemical carcinogens, oncogenic viruses, hereditary factors, irradiation, and chronic trauma, multiple psychological factors are also important. Among these are psychological depression, impaired emotional outlets, and perceived lack of closeness to parents. The effect of addressing these factors in addition to standard medical management is an important question to be answered. A pilot study is in progress, in which patients with medically advanced malignant disease are being counseled in addition to receiving appropriate medical treatment. Standard mental health processes of counseling are employed in a combination of individual and group counseling sessions. From 1974 through 1978, a total of 193 patients with medically advanced malignant disease have received counseling in addition to their medical treatment. The three most frequent diagnoses are breast cancer (71), bowel cancer (28), and lung cancer (24). These are also the three most common diagnoses in the United States. In this study we have observed median survival times of 38.5 mo in advanced breast cancer, 22.5 mo in advanced bowel cancer, and 14.5 mo in advanced lung cancer. These survival times are considerably longer than expected median survival times reported in the literature. Our primary concern in using this approach was that the counseling be helpful and not detrimental to the duration of life, quality of life, and quality of death of the individual. Preliminary results indicate that counseling can be helpful and can also be detrimental, depending upon the dynamics of the relationships among the counselor, the patient, the medical team and the family. This is a preliminary study, and many major questions remain unanswered. (Author abstract) (51 Refs)

7. EPIDEMIOLOGICAL STUDIES INTO THE POSSIBLE CARCINOGENICITY OF HAIR DYES.

Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

Epidemiological studies of the carcinogenicity of hair dyes are complicated by (1) too broad a definition of occupation, with hazards to specific job categories being overlooked, and too narrow a definition, making the surveyed group too small to yield significant results, (2) exposure to competing or cooperating carcinogens, (3) uncertain influence of life style, (4) latency period and changes in occupation, and (5) changes and regional variations in occupational classification. A review of reports on cancer incidence among barbers, hairdressers, and their customers is made with respect to urinary bladder, lung, larynx, and breast. The evidence is still apparently insufficient to support a link between exposure to hair dye and cancer. Further research with more statistically valid sampling is recommended. (30 Refs)

8. MULTIPLE PRIMARY CANCERS (DOUBLE CANCERS) - REPORT OF SEVEN CASES.

Okubo S, Shintani M, Kokawa T, Okamoto Y, Okubo H
First Dept. Internal Medicine, Kansai Medical Univ., Moriguchi, Japan
Gan No Rinsho; 27(11):1388-1390 1981

Four patients (3 men, 1 woman; 28-70 yr old) with multiple primary cancers, fulfilling the Warren criteria for multiple tumors, and three men 47-78 yr old with multiple cancers that were combinations of cancer tumors and hemopoietic tumors were reported. The hemopoietic tumors were chronic lymphocytic leukemia, chronic myelocytic leukemia, and multiple myeloma. The non-hemopoietic tumors were gastric cancer (3 patients), lung cancer (2); bilateral lung cancer (1), skin cancer (2), and one case each of pancreatic cancer, breast cancer, and maxillary cancer. The period between the diagnosis of of the first and second tumors was less than 6 mo in three patients and from 1 yr 4 mo to 7 yr in four patients. Peripheral blood lymphocytes were greater than 1,000/cubic mm in all of the patients except for the one with chronic lymphocytic leukemia, and positive purified protein derivative and phytohemagglutinin tests were observed in 4/4 and 3/4, respectively, of the patients tested. Of the five patients whose family histories were reviewed, two had parents who had died of canc[illegible] the two patients with lung cancer had histories of smoking 20 cigarettes/day. (14 Refs) (In JPN)

POSSIBLE IATROGENIC FACTORS IN HUMAN BREAST CARCINOGENESIS

9. A PROSPECTIVE COHORT STUDY OF ORAL CONTRACEPTIVES AND BREAST CANCER.

Trapido EJ
Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115
JNCI; 67(5):1011-1015 1981

In 1970 a questionnaire was sent to 97,300 married women aged 25-50 yr residing in eastern Massachusetts. Information was requested on use of oral contraceptives (OC), education, and gynecologic and reproductive histories. Subsequent questionnaires were sent in 1973 and 1979 to a subset of the original cohort (37,000) to obtain recent information. Surveillance of 34 hospitals disclosed 622 cases of breast cancer among respondents diagnosed in a 6-1/2 yr period. The rate ratio of breast cancer associated with any use of OC was 0.84 (95% confidence limits: 0.7, 1.1). Although certain subgroups of users experienced significantly lower rates of hospitalization for breast cancer than did nonusers (including users aged 25-29, those for whom less than or equal to 5 yr had passed since first use, women with ages at birth of first child either before 25 or after 30, and women who first used OC after the birth of the first child), the risk of breast cancer was not consistently lower among users of OC. Among nulliparous women, the rate ratio associated with use of OC was 2.1 (0.9, 5.0). (Author abstract) (20 Refs)

10. BREAST AND OTHER CANCER DEATHS IN A MENTAL HOSPITAL.

Costa D, Mestes E, Coban A
G. Marinescu Hosp., R-75622 Bucharest, Romania
Neoplasma; 28(3):371-378 1981

The neuroleptics, well known as stimulants of prolactin release, are supposed to increase breast cancer incidence. To verify this hypothesis, we selected a group of 853 deaths of female inpatients with mental diseases recorded in the Dr G Marinescu Hospital between 1929 and 1978. Using proportionality and indirect standardization methods, we did not find any association between the incidence of breast cancer death and neuroleptic therapy, widely used in the above-mentioned hospital after 1959. Several authors reported a low cancer death incidence in mental patients. Between 1925 and 1978, 2,168 deaths were recorded in this hospital. Besides death certificates, we also studied 1,444 complete autopsy protocols (66.60% of all the deaths). Cancer deaths represented 1.94% of 1,231 deaths recorded between 1925 a nd 1960. Cancer deaths represented 7.04% of 937 deaths in the period 1961-1978, in comparison with 13.36% of the whole population of Romania (p less than 0.001). Among these 937 deaths, statistically significant lower cancer ratios than in the general population were found in 10-yr age groups, ie between 15 and 74 yr in women and between 45 and 74 yr in men. No case of leukemia was recorded over 1925-1978. Deaths from pneumonia, bronchopneumonia and cardio-vascular diseases are now frequent in major mental disorders. New prospective studies are required to elucidate the problem of cancer incidence in mental patients. (Author abstract) (19 Refs)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

11. PROPHYLAXIS OF MAMMARY NEOPLASIA BY SELENIUM SUPPLEMENTATION IN THE INITIATION AND PROMOTION PHASES OF CHEMICAL CARCINOGENESIS.

Ip C
Dept. Breast Surgery, Breast Cancer Res. Unit, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Res; 41(11,part1):4386-4390 1981

The present study was designed to determine the chemopreventive effect of dietary selenium supplementation in the initiation or promotion phase of 7,12-dimethylbenz[a]anthracene-induced mammary carcinogenesis in rats fed a high-fat diet. Control animals received 0.1 ppm of selenium (as sodium selenite), while experimental groups were supplemented with 5 ppm of selenium for various periods of time:-2 to +24,-2 to +2, +2 to +24, +2 to +12, +12 to +24, and-2 to +12. The time of 7,12-dimethylbenz[a]anthracene administration (50 days of age) was taken as Time 0, minus and plus signs represent the time in wk before and after 7,12-dimethylbenz[a]anthracene administration, respectively. The following conclusions were drawn from the results: (a) selenium can inhibit both the initiation and promotion phases of carcinogenesis; (b) a continuous intake of selenium is necessary to achieve max inhibition of tumorigenesis; (c) the inhibitory effect of selenium in the early promotion phase is probably reversible; and (d) the efficacy of selenium is attenuated when it is given long after carcinogenic injury. In addition, the present investigation also assessed the effectiveness of selenium in inhibiting the reappearance of mammary tumors that had regressed after ovariectomy. By supplementing tumor-bearing animals with 5 ppm of selenium in the diet immediately after endocrine ablation, it was found that tumors reappeared at a slower rate compared to the controls. The data suggested that selenium is not only effective in chemoprevention but can also be used as an adjuvant chemotherapeutic agent. (Author abstract) (35 Refs)

12. DIETARY SELENIUM INTAKE AND GROWTH OF THE MT-W9B TRANSPLANTABLE RAT MAMMARY TUMOR.

Ip C, Ip MM, Kim U
Dept. Breast Surgery, Roswell Park Memorial Inst., Buffalo, NY, 14263
Cancer Lett; 14(1):101-107 1981

The effect of dietary selenium deficiency and supplementation on the growth of the transplantable MT-W9B mammary carcinoma in syngeneic Wistar-Furth female rats was investigated. The rats were fed a high fat diet (25% corn oil) supplemented with either less than 0.02 ppm, 0.1 ppm, or 2 ppm selenium. Selenium deficiency caused a drastic reduction in the activity of hepatic glutathione peroxidase, while excess selenium had little effect on its activity. Palpable tumors appeared earlier in the rats given less than 0.02 ppm or 0.1 ppm selenium, compared to those given 2 ppm. Dietary selenium at 2 ppm reduced the tumor wt by approx 50% compared to that in the 0.1 ppm group. No histological change in the tumors accompanied with the wt decrease. It is suggested that the inhibitory effect of selenium is selective, without inducing any wt loss or any recognizable toxicity in the animals. (25 Refs)

13. MELATONIN INHIBITION AND PINEALECTOMY ENHANCEMENT OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS IN THE RAT.

Tamarkin L, Cohen M, Roselle D, Reichert C, Lippman M, Chabner B
Intramural Res. Program, Natl. Inst. Child Health and Human Development, NCI, NIH, Bethesda, MD, 20205
Cancer Res; 41(11,part1):4432-4436 1981

The effects of the pineal hormone, melatonin, and of pinealectomy on the incidence of mammary adenocarcinoma in Sprague-Dawley rats treated with 7,12-dimethylbenz(alpha)anthracene (DMBA) were investigated. Melatonin (2.5 mg/kg), begun on the same day as DMBA (15 mg) treatment and given daily in the afternoon for 90 days, significantly reduced the incidence of mammary tumors from 79% (control) to 20% (treated) (p less than 0.002). Rats pinealectomized at 20 days of age and treated with 7 mg of DMBA at 50 days of age had a higher incidence of tumors (88%) compared to control animals (22%). Fifteen mg of DMBA, which resulted in a higher incidence of tumors, reduced the difference between pinealectomized and control animals. Melatonin only partially reversed the effects of pinealectomy, reducing the incidence from 87% (pinealectomy alone) to 63% (pinealectomy plus melatonin); however, the tumor incidence was still lower (27%) in nonpinealectomized, melatonin-treated animals. Assessment of plasma prolactin, luteinizing hormone, follicle-stimulating hormone, estradiol, and cortisol in DMBA-treated tumor-free and tumor-bearing animals revealed a significantly lower plasma prolactin concentration [27 +-5 (SE)ng/ml] in melatonin-treated animals as compared to vehicle-treated animals [65 +-8 ng/ml]. The concentration of plasma prolactin was less in melatonin-treated, pinealectomized rats (55 +-10 ng/ml) as compared to vehicle-treated, pinealectomized animals (101 +-13 ng/ml). Other hormones were not affected by melatonin treatment. These data support the hypothesis that melatonin inhibits the development of DMBA-induced mammary tumors in the rat while removal of the pineal gland stimulates development of such tumors. Additionally, these experiments provide evidence that these effects may be mediated by a suppression of plasma prolactin levels. (Author abstract) (28 Refs)

14. STRUCTURAL ALTERATIONS WITHIN N-NITROSOMETHYLUREA-INDUCED MAMMARY TUMORS AFTER IN VIVO TREATMENT WITH CIS-HYDROXYPROLINE.

Strum JM, Lewko WM, Kidwell WR

Dept. Anatomy, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201

Lab Invest; 45(4):347-354 1981

N-Nitrosomethylurea-induced mammary tumors in Buffalo rats were examined ultrastructurally and compared with tumors from rats treated in vivo for 9 days with cis-hydroxyproline (CHP). The tumors from untreated animals were heterogeneous histologically but often had their cells arranged in clusters called pseudolobules. At the periphery of the pseudolobules in control tumors, a few myoepithelial cells showed evidence of basal lamina secretion. Outlining the pseudolobules were many mast cells. Treatment with CHP inhibited the growth of the tumors. It increased the extent of atrophy and regression and also induced cyst-like areas to form within the pseudolobules. These 'pseudocysts' were actually part of the stromal compartment and they sometimes contained multilayered basal lamina and mast cells. The extensive multilayering of the basal lamina observed after CHP-treatment was thought to arise from extensive infoldings as the pseudolobules 'shrank' due to atrophy and loss of cells. The multilayering and cell debris disappeared from the pseudocysts, leaving many spaces bounded by myoepithelial cells. The remaining myoepithelial cells appeared atrophied, but often had an expanded rough endoplasmic reticulum. We did not observe evidence of basal lamina secretion by cells in treated tumors, which correlates with CHP's ability to block Type IV collagen production. (Author abstract) (35 Refs)

15. RELATIONSHIP OF METABOLIC ACTIVATION OF N-HYDROXY-N-ACYLARYLAMINES TO BIOLOGICAL RESPONSE IN THE LIVER AND MAMMARY GLAND OF THE FEMALE CD RAT.

Shirai T, Fysh JM, Lee M, Vaught JB, King CM
(c/o King) Dept. Chemical Carcinogenesis, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 41(11,part1):4346-4353 1981

Ip injection of the N-formyl, N-acetyl, or N-propionyl derivatives of N-hydroxy-4-aminobiphenyl, N-hydroxy-2-acetylaminofluorene, or N-(4-biphenyl)glycolamide disclosed that the ability of these compounds to induce mammary tumors in the female CD rat was greater if the compound was able to be metabolized to a reactive product by one of two soluble enzymes obtained from both the liver and mammary gland. A similar but weaker association between the formation of gamma-glutamyltranspeptidase-positive foci and cellular altered foci of the liver was also observed. The enzyme related to the tumorigenicity of these compounds was characterized by a highly specific capacity to form adducts from the acetyl and propionyl derivatives. The other enzyme exhibited greater activity with N-formyl substrates. The two enzyme activities were separable by ion-exchange chromatography on DEAE-cellulose and by gel filtration of Sephacryl. Liver microsomes also possessed the capacity to activate both the formyl and acetyl derivatives to reactive species; formyl substrates were 7 to 8x more active than acetylated compounds. The microsomal activities and the formyl-preferring soluble enzyme were inhibited by diethyl-p-nitrophenylphosphate, a microsomal deacylase inhibitor. The cytosolic enzymes that are most active with the acetyl and propionyl substrates were little affected by this organophosphate compound. The microsomal activation was not due solely to deacylation of the hydroxamic acids, since formylated and acetylated substrates were hydrolyzed at approx the same rates. (Author abstract) (37 Refs)

16. DIFFERENTIAL EFFECT OF SEVERAL INDUCERS ON HEPATIC AND MAMMARY BENZO(A)PYRENE METABOLISM IN RAT AND HAMSTER.

Gingell R, Weber A, Ilacqua V, Van de Walle C, Hertzog P
Shell Development Co., Westhollow Res. Center, P. O. Box 822, Houston, TX, 77001
Drug Chem Toxicol; 4(2):101-112 1981

The ability of female Sprague Dawley rat and Syrian golden hamster mammary microsomes, as compared with the liver, to metabolize benzo(a)pyrene (BP) was examined in an attempt to understand the different susceptibilities of these species to polynuclear hydrocarbon-induced mammary tumorigenesis. The effect of pretreatment with several known mixed function oxidase inducers on these activities was studied in both species. Control hamster hepatic benzo(a)pyrene-hydroxylase (BPH) activity was considerably greater than that of the rat. Aroclor was the only inducer to significantly increase hamster hepatic BPH activity, and this by only two-fold. 7,12-dimethylbenz(a)anthracene and 3-methylcholanthrene had no effect on hamster liver BPH activity while beta-naphthoflavone (BNF) slightly inhibited this activity. All compounds examined were potent inducers of hepatic BPH and cytochrome P450 in the rat. Control hamster mammary microsomal BPH activity was much lower than the hepatic level, but was fourfold greater than the corresponding level for the rat. All the pretreatments caused similar increases in mammary activity in both species, BNF being the most effective. The ability of control hamster hepatic microsomes to metabolize BP was considerably greater than for the rat. The results indicated that rat and hamster mammary gland microsomes, as well as those of liver, are capable of metabolizing BP. All the pretreatments investigated induced mammary activity in both species, but the rat activity was more inducible than that of the hamster. It was therefore suggested that metabolic activation of carcinogenic polycyclic hydrocarbons can occur in the mammary gland itself. (16 Refs)

17. EXPERIMENTAL TOXICOLOGY OF THE AROMATIC RETINOID RO 10-9359 (ETRETINATE).

Teelmann K

Biologisch-Pharmazeutische Forschung, F. Hoffmann-La Roche and Co. AG, Grenzacherstrasse 124, CH-4002 Basel, Switzerland

Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

Acute toxicity studies in rats, mice, and dogs and subacute and chronic toxicity studies in rats and dogs were performed using the spray-dried form of Ro 10-9359 (Etretinate) given by different routes. A 2-yr study revealed no carcinogenic potential of Ro 10-9359 in the rat; in fact, the number of rats bearing multiple tumors was less in the intermediate and high dose groups than in controls, and the number and variation of mammary tumors in the high-dose females (3 mg/kg/day) was significantly less than in the female controls. (18 Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

18. ON THE OCCURRENCE AND TRANSPORT OF ESTRIOL-3-SULFATE IN HUMAN BREAST CYST FLUID: THE METABOLIC DISPOSITION OF BLOOD ESTRIOL-3-SULFATE IN NORMAL WOMEN.

Raju U, Noumoff J, Levitz M, Bradlow HL, Breed CN

(c/o Levitz) Dept. Obstetrics-Gynecology, New York Univ. Medical Center, 550 First Ave., New York, NY, 10016

J Clin Endocrinol Metab; 53(4):847-851 1981

The high concentration of estriol-3-sulfate (E3-3S) in human breast cyst fluid has been confirmed in 14 women with multiple cysts. The concentrations of E3-3S found in individual cysts drained within a short time span from the same patient were variable, the ratios ranging from unity to 40. After the iv administration of [14C]estriol or [3H]E3-3S, only minor accumulation of either isotope was detected in the cyst fluids aspirated 6.5-30 hr later. Since surprisingly small amounts of isotopes were found in blood, the metabolism of [3H]E3-3S was studied in two normal women. The test compound was injected iv, and blood samples were taken at intervals up to 7.5 hr. In addition, total urine was collected for 3 days. The blood clearance of [3H]E3-3S was rapid, with the half-life ranging from 15-30 min. However, E3-3S was only a minor component of the urine indicating rapid tissue extraction and metabolism rather than renal excretion for the compound. The studies indicate that E3-3S of human breast cyst fluid does not equilibrate rapidly with other body pools and that its uptake, if any, from the blood would be against a gradient. (Author abs tract) (22 Refs)

19. DETECTION OF HUMAN PLACENTAL LACTOGEN IN SERA AND TUMOURS OF PATIENTS WITH FIBROADENOMA OF BREAST.

Sheth NA, Adil MA, Suraiya JN, Sheth AR

Cancer Res. Inst., Parel, Bombay 400 012, India

Br J Cancer; 44(2):258-261 1981

While human placental lactogen (hPL) has been reported associated with malignant tumor, a study is presented which shows its presence in sera of 9/30 women with fibroadenoma of the breast while it was not detected in 30 normal non-pregnant women and 30 normal men. A sensitive radioimmunoassay was used for determination of hPL in tumor extracts and pre- and postoperative sera from patients. In a study of tumors from 21 patients, 9 extracts were positive for hPL. These nine patients (6 with unilateral and 3 with bilateral tumors) also showed hPL in preoperative sera. Twelve other patients (9 with unilateral and 3 bilateral tumors) showed no circulating hPL. Postoperative sera from seven of the nine patients with hPL in their tumors and preoperative sera became negative for hPL 1 wk to 6 mo after excision of fibroadenoma. In the case of bilateral tumors, the presence of hPL in both breasts suggests the possibility of a common factor governing ectopic secretion in both sites. The study indicated a greater production of hPL than beta human chorionic gonadotropin (beta-hCG) in sera of patients with fibroadenoma of the breast. These reports suggest a key role for hPL in the etiology of human benign breast tumors. (13 Refs)

20. DIFFERENT EFFECTS OF OESTRADIOL, OESTRIOL, OESTETROL AND OF OESTRONE ON HUMAN BREAST CANCER CELLS (MCF-7) IN LONG TERM TISSUE CULTURE.

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Acta Endocrinol (Copenh); 98(1):73-80 1981

The effects of estradiol (Oe2), estrone (Oe1), estriol (Oe3), estetrol (Oe4) on the induction of the progesterone receptor (PgR) and growth of MCF-7 cells are compared. All the four estrogens increase cell PgR concentration. Analysis of the dose-response curves shows induction by Oe2 to be 10x and 50x greater than Oe3 and Oe4, respectively. Oe1 and Oe2 are equally effective, even with consideration of metabolic conversion of Oe1 into Oe2. When compared with untreated cells, Oe2, Oe3 and Oe4 do not influence significantly the plating efficiency but all three hormones increase thymidine incorporation of cells in log phase growth. Oe2, Oe3 and Oe4 are able to rescue the growth inhibition induced by antiestrogens. The respective potency compared to Oe2 is again in the range of 10 and 50x lower for Oe3 and Oe4, respectively. On the other hand Oe1 decreases plating efficiency, thymidine incorporation and does not rescue the growth inhibition induced by antiestrogens when the metabolic conversion of Oe1 into Oe2 is prevented. Thus, Oe3 and Oe4 behave like complete Oe2 agonists whereas Oe1 has dissociated effects, agonist on PgR induction and antagonist on cell growth. (Author abstract) (24 Refs)

21. PLASMA CONCENTRATIONS OF C-19 STEROIDS, ESTROGENS, FSH, LH AND PROLACTIN IN POST-MENOPAUSAL WOMEN WITH AND WITHOUT BREAST CANCER.

Bird CE, Cook S, Owen S, Sterns EE, Clark AF
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Oncology; 38(6):365-368 1981

The plasma levels of 5alpha-dihydrotestosterone, testosterone, delta5-androstene-3beta,17beta-diol, delta4-androstenedione, dehydroepiandrosterone, estrone, estradiol, dehydroepiandrosterone sulfate, follicle stimulating hormone, luteinizing hormone and prolactin were measured in normal post-menopausal women and in post-menopausal women with proven breast cancer. The mean prolactin level was significantly higher (p less than 0.01) and the mean 5alpha-dihydrotestosterone level lower (p less than 0.05) for the women with breast cancer. There were no significant differences for any of the other hormones. As well, there were no significant differences for the extent of binding of testosterone and delta5-androstene-3beta,17beta-diol to plasma proteins between the two groups of subjects. (Author abstract) (29 Refs)

22. SERUM ANDROGEN LEVELS AND THE MENSTRUAL CYCLE IN WOMEN WITH BENIGN OR MALIGNANT BREAST DISEASE.

England PC, Sellwood RA, Knyba RE, Irvine JD
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Clin Oncol; 7(3):213-219 1981

Serum levels of dehydroepiandrosterone sulfate have been determined in blood specimens taken over the menstrual cycle in 10 normal women and 28 patients with benign and malignant breast disease. There was no consistent or statistically significant correlation between the amounts of serum dehydroepiandrosterone sulfate and estradiol. This finding does not support the suggestion that the subnormal levels of androgens, in women with high risk of breast cancer and patients with a poor prognosis, reflect alterations in estrogen secretion. (Author abstract) (19 Refs)

23. AN ANTIESTROGENIC ACTION OF ANDROGENS IN HUMAN BREAST CANCER CELLS.

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Dept. Medicine, 3E-17, Veterans Admin. Medical Center, Iowa City, IA, 52240
J Clin Endocrinol Metab; 53(4):836-842 1981

We have recently observed that androgens prevent the estrogen-dependent augmentation of cytoplasmic progesterone receptor (PRc) in MCF-7 human breast cancer cells and now report the results of studies that further characterize this new example of sex steroid antagonism. Using a single saturating dose assay to monitor changes in MCF-7 PRc concentration, we have observed that androgens are capable of inhibiting both the estrogenic induction and the ongoing stimulation of PRc synthesis, but have no apparent effect upon basal concentrations of this receptor. Both testosterone and dihydrotestosterone (DHT) demonstrate similar degrees of antiestrogenic activity at concentrations between 10(-10)-10(-8) M. Furthermore, a 10(-8)-M concentration of either androgen completely inhibits the stimulation of PRc synthesis by 10(-11)-10(-8) M 17beta-estradiol (E2). This inhibitory effect is maintained during the continued presence of either testosterone or DHT, but rapidly disappears after the withdrawal of androgen from the culture medium. The specific nuclear binding of 17beta-[3H]estradiol over time appears to be similar in cultures incubated in the presence and absence of 10(-8) M DHT. This observation suggests that androgens do not inhibit estrogen action by interfering with the formation, activation, nuclear binding, or nuclear processing of estrogen-receptor complexes. The estrogenic stimulation of PRc is not diminished by the 5beta-epimer of DHT, and the inhibitory activity of DHT itself is blocked by several different antiandrogens. These findings provide substantial support for the concept that the antiestrogenic effect of androgens is mediated by an androgen receptor mechanism. These results may provide new insights into the clinically apparent antagonistic effects of estrogens and androgens upon both normal and malignant human breast tissues. (Author abstract) (21 Refs)

24. DEXAMETHASONE EFFECT ON THE GROWTH RATE, THE PLASMINOGEN ACTIVATOR, AND THE MMTV DEPENDENT DNA POLYMERASE IN A MOUSE MAMMARY TUMOR CELL LINE.

Failly-Crepin C, Fromont S, Crepin M
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Biochem Biophys Res Commun; 102(1):22-29 1981

The effect of dexamethasone (DMS) was studied in cultured cells of murine mammary gland carcinoma (GR cells). DMS caused inhibition of exponential growth but not overall protein synthesis. Treatment with DMS resulted in significant inhibition of extra- and intracellular plasminogen activator. Reverse transcriptase associated with secreted murine mammary tumor virus particles was strongly stimulated. (20 Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

25. IDENTIFICATION OF MOUSE MAMMARY EPITHELIAL CELLS BY IMMUNOFLUORESCENCE WITH RABBIT AND GUINEA PIG ANTIKERATIN ANTISERA.

Asch BB, Burstein NA, Vidrich A, Sun TT
Dept. Exp. Pathology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Proc Natl Acad Sci USA; 78(9,part2):5643-5647 1981

Few markers are available to identify the three types of mammary epithelial cells - ductal, alveolar, and myoepithelial - especially in pathological conditions and in cell cultures. We have used antisera to human keratins in immunofluorescence to facilitate the identification of the three mouse mammary epithelial cell types. In frozen tissue sections and primary cell cultures, a rabbit antikeratin antiserum specifically stained cytoplasmic filaments in all three types of epithelial cells. A guinea pig antiserum against the same keratin preparation, however, reacted preferentially with filaments in myoepithelial cells and readily detected this cell type in normal, dysplastic, and malignant mammary tissues and cell cultures. Neither antisera reacted with fibroblasts or any other mesenchymal cells. The combined use of the two antikeratin antisera thereby permits rapid surveys of tissue sections and cultures for the localization of not only all epithelial cells but also the subpopulation of myoepithelial cells. Moreover, when mammary cultures established from late-pregnant or lactating mice were stained simultaneously with guinea pig antikeratin and rabbit anticasein antisera, three populations of epithelial cells were mutually exclusive: those stained by anticasein antiserum, those stained by guinea pig antikeratin antiserum, and those stained by neither, consistent with properties of alveolar, myoepithelial, and ductal cells, respectively. These antisera thus offer a tool for studying different epithelial cell types during mammary development, tumorigenesis, and malignant progression. (Author abstract) (31 Refs)

26. VALUE OF CARCINOEMBRYONIC ANTIGEN DETERMINATION IN MAMMARY CANCER.

Carrion P, Avila C, Massieu C, Curto M
Seccion Oncologia Medica, Centro Especial 'Ramon y Cajal', Madrid, Spain
Oncologia; 6(4):14,17-18,20-21 1981

Carcinoembryonic antigen (CEA) determination for early diagnosis of relapse after mastectomy and for monitoring effects of hormone and/or chemotherapies is evaluated. Of 140 mammary cancer patients, 9 with localized cancer were tested before and after surgery (Group I), 79 with localized cancer were tested 1, 3, 6, 12, and 24 mo after surgery (Group II), and 52 with advanced cancer (5 having distant metastases) were tested 10-21 days after the end of therapy (Group III). All patients received Halsted or Patey radical mastectomy; axillary adenopathies were examined histologically. Lymph node-positive patients received polychemotherapy and antiestrogen therapy for 6 mo. Patients with metastases were treated with different hormone therapy and chemotherapy. In Group I five patients exhibited elevated CEA which became normal after surgery, but later three of them developed metastases. In Group II 67 patients remain clinically free of disease, although 10 had elevated CEA values (greater than 50 mg in 2 cases). The remaining 12 patients developed metastases although CEA was normal in 8 and elevated in 4; 11 of the patients had axillary metastases with greater than 4 positive lymph nodes. In Group III 33 patients had elevated CEA (greater than 25 mg in 25 cases). CEA was elevated in 100% of hepatic, 83.3% of lung, and 72.2 % of bone metastasis cases. Hormone therapy and/or chemotherapy was monitored in 25 patients; 80% of remissions and relapses could be followed by CEA. (12 Refs) (In SPA)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

27. QUANTITATION OF MURINE MAMMARY TUMOR VIRUS-RELATED RNA IN MAMMARY TISSUES OF LOW- AND HIGH-MAMMARY-TUMOR-INCIDENCE MOUSE STRAINS.

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J Virol; 40(1):87-95 1981

Lactating mammary glands and hormonally induced mammary tumors of BALB/c mice from three geographically separated breeding colonies were examined by molecular hybridization, using murine mammary tumor virus (MuMTV)cDNA representing the entire viral genome to determine the amount of MuMTV-related RNA expressed in these tissues. The RNA extracted from these tissues by the classical sodium dodecyl sulfate-pronase, phenol-chloroform procedure (method 1) contained barely detectable levels of MuMTV-related sequences. In contrast, both normal lactating mammary glands and hormonally induced mammary tumors of these mice were found to contain approx one to two copies of the MuMTV genome per cell by using a new procedure in which the RNA was extracted with guanidine derivatives (method 2). No significant differences in the MuMTV-related RNA content of the BALB/c mammary tissues were observed regardless of their colony of origin. Our results suggest that expression of MuMTV RNA does not change in BALB/c mammary glands during transformation to a malignant state and that MuMTV expression does not play a role in tumorigenesis in these mice. In view of the increased recovery of MuMTV-related RNA from BALB/c mice with method 2, we compared the level of MuMTV RNA expression in lactating mammary glands and mammary tumors of other mouse strains, including C57BL/6 and RIII, using both extraction methods. Yields of MuMTV-related RNA from mammary tissues increased by as much as 35-to 40-fold, using method 2 as compared with method 1. Therefore method 2, involving guanidine derivatives, appears to be the method of choice for MuMTV-related RNA extraction from the mammary tissues of certain strains of mice, particularly those expressing relatively low levels of MuMTV RNA. (Author abstract) (20 Refs)

28. USE OF AN ELECTROIMMUNODIFFUSION METHOD ON CELLULOSE ACETATE FILMS FOR THE DETECTION OF ANTIGENICITY IN HUMAN BREAST CANCER THAT IS RELATED TO THE MAJOR CORE ANTIGEN OF MOUSE MAMMARY TUMOR VIRUS (MUMTV).

Kryukova IN, Komarova E, Zotter S, Grossmann H
All Union Cancer Res. Center, Acad. Medical Sciences, Kashirskoye Chausse 6, Moscow 115478, USSR
Arch Geschwulstforsch; 51(6):517-521 1981

The method developed by Abelev was used for detection of MuMTV-related antigens in tumor tissue and sera of breast cancer patients. The highly sensitive electroimmunodiffusion method on ac etate films employed isotachophoresis. In 2/5 breast cancer extracts, protein fractions of about 50,000 mol wt exhibited antigenicity related to the major core antigen of MuMTV (p27). This antigenicity was not detected in the patients' sera. (18 Refs)

29. IMMUNOLOGICAL CHARACTERIZATION OF A LOW ONCOGENIC MOUSE MAMMARY TUMOR VIRUS FROM BALB/CNIV MICE.

Vacquier JP, Cardiff RD, Blair PB
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J Virol; 40(1):56-64 1981

Antigenic determinants of mouse mammary tumor virus (MuMTV) from the low-mammary-tumor-incidence strain BALB/cNIV were compared by competition radioimmunoassay with those of MuMTV's isolated from several high- and low-mammary-tumor-incidence mouse strains, using rabbit hyperimmune sera against BALB/cNIV MuMTV and against MuMTV from the high-mammary-tumor-incidence strain BALB/cfC3H. Using anti-BALB/cfC3H serum in competition radioimmunoassay, BALB/cNIV MuMTV lacked antigenic determinants present on MuMTV's from the BALB/cfC3H, C3H, and GR strains. With anti-BALB/cNIV serum in competition radioimmunoassay, type-specific antigenicity was detected with BALB/cNIV MuMTV. We found class-specific antigenicities on BALB/cNIV MuMTV that were shared with RII and C3Hf MuMTV'S. BALB/cNIV MuMTV was reportedly derived from the C3Hf strain by infection of BALB/c mouse mammary tissue after transplantation into a (BALB/c x C3Hf)F1 hybrid followed by retransplantation into the BALB/c strain. However, BALB/cNIV MuMTV contained type-specific antigens not present on C3Hf MuMTV. The possible origin of these determinants is discussed. (Author abstract) (31 Refs)

RADIOLOGICAL ASPECTS OF MAMMARY GLAND CARCINOGENESIS

30. IMPLICATIONS OF NEW HIROSHIMA AND NAGASAKI DOSE ESTIMATES: CANCER RISKS AND NEUTRON RBE.

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Health Phys; 41(4):666-671 1981

Dose-response relations for radiation-induced leukemia, breast cancer, total malignancies, and chromosome aberrations in atomic bomb survivors were analyzed with the use of new dose estimates that differ substantially from the generally accepted values. They indicate that the gamma ray component and total dose were higher in Hiroshima than previously believed and lower in Nagasaki; neutron components were lower in both cities. Dose-response curves for leukemia and breast cancer were similar in the two cities, but those for total malignancies and chromosome aberrations demonstrated significant inter-city differences. The inter-city differences were due to an increase in neutron relative biological effectiveness (RBE) with decreasing dose due to diminished gamma-ray effectiveness. The neutron RBE for leukemia and breast cancer induction remain to be clarified. (13 Refs)

31. STRESS AND RADIATION CARCINOGENESIS IN MICE.

Kalisnik M, Vraspir-Porenta O, Kham-Lindtner T, Logonder-Mlinsek M, Skrk J, Pajntar M
Inst. Histology and Embryology, Univ. E. Kardelj Ljubljana, 61105 Ljubljana, Yugoslavia
Neoplasma; 28(3):275-279 1981

In the present experiment irritation consisting of a combination of an optic signal followed by a mild electroshock administered at regular intervals, was started in two groups of animals at the age of 3 mo. At 4 mo of age, one of the irritated and one of the nonirritated groups were exposed to whole-body gamma irradiation at 20 daily doses of 0.5 Gy (50 rad), 1.4 Gy/min (140 rad/min), while the other two groups were sham-irradiated. The animals were autopsied and the specimens were microscopically studied for the presence of malignant tumors. Malignant tumors involving particularly the testes and lungs and leukosis were found in 29% of males, whereas in females the tumor incidence with the mammary, pulmonary and ovarian involvement and leukosis was 39%. The irradiation decreased the minimum latency time in the irritated males and both female groups. In males, the irritation lowered the cumulative prevalence of malignant tumors, a significant decrease being noted at the age of 15 mo. In females, it was increased, with a significant rise observed to occur at the end of the experiment. The opposite effects of irritation on the radiation carcinogenesis in males and females can be attributed to the irradiation-induced specific alterations of the gonads in females and, in part, to a longer survival time observed in the irradiated females. (Author abstract) (12 Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

32. BENIGN SPINDLE CELL BREAST TUMOR.

Toker C, Tang CK, Whitely JF, Berkheiser SW, Rachman R
Dept. Pathology, Univ. Maryland Hosp., 22 South Greene St.. Baltimore, MD, 21201
Cancer; 48(7):1615-1622 1981

A distinctive, benign, spindle cell tumor of the breast is described. Three patients were men, the fourth a woman. Histologically, each tumor displayed islands of spindle or stellate cells embedded in a collagenous matrix. Within the female breast, the lesion was within the stroma, displacing but not including the epithelial elements. Ultrastructural study of two tumors revealed diverse populations composed of fibroblasts, myofibroblasts, smooth muscle cells, and undifferentiated mesenchymal cells. The relationship of these tumors to spindle cell lipomas is discussed. The lesions have all been clinically benign, and their recognition as such is important. (Author abstract) (1 Ref)

33. BIOCHEMICAL SUBGROUPING OF BENIGN BREAST DISEASE TO DEFINE PREMALIGNANT POTENTIAL.

Minton JP, Abou-Issa H, Elliot JB, Foecking MK, Roseman JM, Matthews RH
Dept. Surgery, Ohio State Univ., 410 W. 10th Ave., Columbus, OH, 43210
Surgery; 90(4):652-656 1981

To determine which subgroups of benign breast disease are likely to progress to malignant degeneration, a biochemical analysis of cyclic AMP (cAMP) was run on several samples of breast tissue. cAMP is elevated in a progressive fashion from normal breast tissue to fibrosis, cystic mastitis, ductular hyperplasias, and finally to carcinoma. Correlation of cAMP levels in breast lesions with histopathologic grading of increasing epithelial proliferation confirmed the concept that there are subgroups within those lesions that have greater malignant potential. Benign breast lesions with significantly higher cAMP levels, although still lower than those of cancer, must be considered at higher risk for eventual malignant change. (Author abstract) (19 Refs)

34. PROBABLE MECHANISM FOR THE LOSS OF BARR BODY IN HUMAN FEMALE TUMOR WITH SPECIAL REFERENCE TO BREAST CANCER.

Ghosh SN, Shah PN
Endocrinology Div., Cancer Res. Inst., Parel, Bombay 400 012, India
Med Hypotheses; 7(8):1099-1104 1981

The relationship between Barr body frequency (BBF) and human female breast tumors is discussed. A decrease in BBF has been observed in colonic neoplasms. This decrease in BBF is possibly related to reactivation of the second X chromosome with concurrent increase in glucose-6-phosphate dehydrogenase activity. Factors that may be involved in the reactivation of a genetically inactive X chromosome are discussed. Studies of post-menopausal women, G-6PD activity in carcinogen-induced rat breast tumors, and estradiol-17beta treatment of HeLa cells indicate an association between BBF frequency and estrogen. Evidence that both X-chromosomes are active in clonal cultures of undifferentiated female mouse teratocarcinoma stem cells derived from spontaneous ovarian tumors has been presented. Other evidence suggesting that activation of a second X-chromosome is not the true mechanism for loss of X-chromatin is presented. Evidence suggesting that low Barr body counts in highly malignant human breast tumor could be related to elaboration of collagenase from tumor cells at the time of invasion is presented. (35 Refs)

35. ACTIVATION OF RELATED TRANSFORMING GENES IN MOUSE AND HUMAN MAMMARY CARCINOMAS.

Lane MA, Sainten A, Cooper GM
Sidney Farber Cancer Inst., Boston, MA, 02115
Proc Natl Acad Sci USA; 78(8):5185-5189 1981

High mol wt DNAs of five tumors induced by mouse mammary tumor virus (MMTV), two mouse mammary tumors induced by a chemical carcinogen, and one human mammary tumor cell line (MCF-7) were assayed for the presence of transmissible activated transforming genes by transfection of NIH 3T3 mouse cells. DNAs of all five MMTV-induced tumors, one chemical carcinogen-induced tumor, and the human tumor cell line induced transformation with high efficiencies (approx 0.2 transformant per ug of DNA). NIH cells transformed by DNAs of MMTV-induced tumors did not contain exogenous MMTV DNA sequences, indicating that MMTV-induced mammary carcinomas contained activated cellular transforming genes that were not linked to viral DNA. The transforming activities of DNAs of all five MMTV-induced tumors, the chemical carcinogen-induced mouse tumor, and the human tumor cell line were inactivated by digestion with the restriction endonucleases Pvu II and Sac I, but not by BamHI, EcoRi, HindIII, Kpn I, or Xho I. These results indicate that the same or closely related transforming genes were activated in six different mouse mammary carcinomas, induced by either MMTV or a chemical carcinogen, and in a human mammary carcinoma cell line. (Author abstract) (25 Refs)

36. SISTER-CHROMATID EXCHANGES IN LYMPHOCYTES IN WOMEN WITH CANCER OF THE BREAST.

Husum B, Wulf HC, Niebuhr E
Dept. Anesthesia, Gentofte Hosp., DK-2900 Hellerup, Copenhagen, Denmark
Mutat Res; 85(5):357-362 1981

Sister chromatid exchanges (SCE) were studied in peripheral blood lymphocytes of 131 patients (17-90 yr old; median 51.8 yr) treated surgically for tumor of the breast. In 52 patients with perioperative histological proof of carcinoma of the breast, the SCE rate (mean +- standard error of the mean) was 9.39 +-0.17; the rate was 9.88 +-0.18 for 79 patients with nonmalignant fibroadenomatosis. Benign or malignant character of the tumor apparently did not influence SCE rate; age, preoperative mammography, and use of oral contraceptives or estrogens also were without significant influence. A statistically significant correlation was found between SCE and cigarette smoking. The 45 cigarette smokers exhibited 10.49 +-0.23 SCE/cell compared with 9.26 +-0.13 SCE/cell found in 86 nonsmoking patients. It is concluded that spontaneous SCE in lymphocytes is not an indicator of carcinoma of the breast. (19 Refs)

37. ABSENCE OF SEASONAL VARIATION OF ESTROGEN RECEPTOR LEVELS IN HUMAN BREAST CANCER TISSUE.

van Landeghem AA, Poortman J, Faber JA, Thijssen JH
Dept. Endocrinology, Univ. Hosp., State Univ. Utrecht, Catharijnesingel 101, Utrecht, The Netherlands
Mol Cell Endocrinol; 23(3):265-273 1981

Between 1975 and 1978, 979 human primary breast cancer tumors (HPBCT) were collected, frozen, within 2 wk cytosol without lipids prepared, and estradiol receptors quantitatively determined by the modified European Organization for Research on the Treatment of Cancer procedure. Of 979 HPBCT, 631 classified receptor positive were derived from 212 premenopausal and 419 postmenopausal patients. Results for the two groups were statistically analyzed separately and combined; analyses do not support the existence of any periodicity in estrogen receptor level with seasonal variation consistent from yr to yr. (16 Refs)

38. FAILURE OF ESTRADIOL IMMUNOFLUORESCENCE IN MCF-7 BREAST CANCER CELLS TO DETECT ESTROGEN RECEPTORS.

Mercer WD, Edwards DP, Chamness GC, McGuire WL
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Cancer Res; 41(11,part1):4644-4652 1981

An indirect immunofluorescence assay was used to detect estradiol in MCF-7 breast cancer cells to determine if the estradiol-specific fluorescence observed represented estrogen receptor-bound estradiol. Appropriate controls were used to demonstrate the immunological specificity of our assay procedures. Initial studies of estradiol binding in MCF-7 cells were performed at 20 C for 1 hr with different concentrations of estradiol. Cytoplasmic and nuclear staining were observed following treatment with 10 nM estradiol, but not with lower concentrations which were nevertheless still sufficient to saturate the estrogen receptor. The staining intensity increased with higher estradiol concentration, which is consistent with estradiol binding to lower-affinity binding sites. In order to further determine if estradiol binding by the estrogen receptor was being detected, we pretreated MCF-7 cells with 5 nM diethylstilbestrol at 37 C for 1 hr to translocate all the estrogen receptor to the nucleus and then administered estradiol at varying concentrations for 4 hr at 4 C. The estradiol was still primarily detected in the cytoplasm, although virtually all of the estrogen receptor was found to be present in the nucleus by standard [3H]estradiol binding assays. Additional immunochemical studies using sucrose gradient analysis to detect antibody-estradiol-receptor complexes clearly established that these complexes could not be detected. The present results suggest that, although immunocytochemical assays can specifically detect estradiol in MCF-7 cells, the estradiol is bound to lower-affinity binding sites rather than to the estrogen receptor. Saturation analyses of intact viable MCF-7 cells performed at 37 C for 30 min using [3H]estradiol at concentrations ranging from 0.1 to 93 nM revealed additional lower-affinity estradiol-binding sites besides the receptor, perhaps analogous to the Type II sites reported in the rat uterus and human breast cancers. (Author abstract) (45 Refs)

39. AUTORADIOGRAPHIC AND ULTRASTRUCTURAL OBSERVATIONS OF PLAQUES AND HORMONE-DEPENDENT MAMMARY TUMORS IN GR MICE.

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Exp Mol Pathol; 35(2):219-230 1981

Hormone-dependent mammary tumors in GR mice, and the disk-shaped 'plaques' from which they originate have been examined by [3H]thymidine labeling and electron microscopy. Plaques consist ed of long narrow, radiating duct-like tubules lined by dark and light secretory cells containing mammary tumor virus (MTV) and underlaid by a few myoepithelial cells. Autoradiographic analysis of plaques revealed a labeling index of 26%, whereas pregnancy-dependent tumors within the same mice had a labeling index of 38%. At the periphery of some tumors plaque-like tubules were evident. Hyperplasia occured (1) within some of these tubules and (2) within nearby alveoli, resulting in cords and clusters of tumor cells. Myoepithelial cells could no longer be identified among the tumor cells. Pregnancy-dependent and hormone-induced tumors both contained club-like extensions having distorted lumens. Intracytoplasmic lamina were sometimes observed as were dark spindle-shaped tumor cells containing MTV. Regression of the tumors was due to rapid cell degeneration which left only a few isolated ducts and/or tubules, some of which presumably have the potential of responding to hormones and initiating another tumor at the same site. (Author abstract) (20 Refs)

40. AUTORADIOGRAPHIC DISTRIBUTION OF HEMATOPORPHYRIN DERIVATIVE IN NORMAL AND TUMOR TISSUE OF THE MOUSE.

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Cancer Res; 41(11,part1):4606-4612 1981

The distribution of isotopically labeled hematoporphyrin derivative (HPD) has been studied in mice bearing the spontaneous mammary tumor (fast growing). In stomach, liver, spleen, and pancreas, 3 hr after ip injection of [3H]HPD, grains were uniformly distributed over the tissue sections. After 24 hr, the grain density overlying parenchymatous areas of these tissues was lower than that over the stromal or reticuloendothelial areas. In the spontaneous mammary tumor (fast growing), higher grain densities were seen over pseudocapsule, stromal septa, and necrotic areas at 3, 6, 12, 24, and 48 hr after injection. At 168 hr postinjection, only isolated stromal cells, presumably macrophages, showed high grain densities. From the temporal changes observed in the distributions of HPD in normal tissues and the relative stability of the distribution seen in the spontaneous mammary tumor (fast growing), we speculate that tissue factors such as vascular permeability, lack of an adequate lymphatic drainage, and nonspecific binding of serum proteins to stromal elements may be responsible for or contribute to the preferential uptake and/or retention of HPD observed in both human and animal tumors. (Author abstract) (32 Refs)

41. RAT MAMMARY CARCINOMA CELLS SECRETE ACTIVE COLLAGENASE AND ACTIVATE LATENT ENZYME IN THE STROMA VIA PLASMINOGEN ACTIVATOR.

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Int J Cancer; 28(4):509-515 1981

A spontaneous mammary adenocarcinoma (AC) from an inbred female rat was investigated with regard to secretion of neutral proteases. Cultures of neoplastic epithelial cells derived from the tumor secreted an enzyme that fulfilled the criteria for a specific collagenase. In contrast to cultures of non-neoplastic cells, tumor collagenase was present as an active enzyme, since treatment with trypsin or p-aminophenylmercuric acetate (APMA) did not increase activity. The neoplastic cells were also prolific producers of plasminogen activator (PA). Dexamethasone (Dex)(10(-6) M) markedly reduced the levels of both enzymes. Addition of tranexamic acid (TA), an inhibitor of plasmin and of plasminogen activation, did not affect collagenase activity, even at 10(-1) M TA, nor did latent collagenase accumulate. Latent collagenase was secreted in culture by normal fibroblasts from neonatal rat lungs. This latent enzyme was activated by the addition of tumor cell medium plus plasminogen, but this effect was inhibited by the addition of TA. These results demonstrate that the neoplastic cells themselves secrete collagenase as an active enzyme. PA is also secreted, is not involved with tumor collagenase, but is capable, in the presence of plasminogen, of activating latent collagenase produced by the non-neoplastic cells within the tumor or in the surrounding tissue. This tumor possesses potent collagenolytic ability in vitro which may be partly responsible for its rapid invasion in vivo. (Author abstract) (36 Refs)

42. CULTURE OF CELLS FROM THE HUMAN BREAST: PROBLEMS AND POTENTIAL.

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Comment Res Breast Dis; 2:87-102 1981

Cell cultures from primary breast cancers are desirable in order to (1) assess the effects of drugs and hormones on tumors, (2) determine the growth characteristics and metabolic properties of normal and malignant cells, and (3) study general growth control to determine why the major human solid tumors arise from epithelium. Breast epithelial cells may be obtained from milk or pleural effusions by centrifugation, or from solid tumors by mechanical or enzymatic disruption followed by selective removal of cells. Epithelial cells may be distinguished in culture from other cell types by appropriate markers, such as antigens. Primary carcinomas contain two general cell types: E cells resemble epithelial cells grown from milk and hyperplastic tissue. E1 cells resemble cells grown from involved lymph nodes and other metastatic tissue. E1 cells have a low mitotic index, are usually lost from culture, and communicate with other cells either indiscriminantly or not at all. E cells have a high mitotic index, are readily cultured, and do not form communicating junctions with human fibroblasts. E1 cells are probably the malignant cells. E1 cultures from lymph node or skin cell are slightly more successful than cultures of E1 cells from primary carcinomas. Nonmalignant cells are often cultured because malignant cell cultures are too often unsuccessful. Human lymphoblastic interferon inhibits the growth of cells that can be cultured from breast tissue and secretions.

The use of other sources of cells other than those from breast tumors, for use in cultures, is discussed. (33 Refs)

43. CLONAL PROLIFERATION OF CULTURED NONMALIGNANT AND MALIGNANT HUMAN BREAST EPITHELIA.

Smith HS, Lan S, Ceriani R, Hackett AJ, Stampfer MR
Dept. Surgery, Albert Einstein Coll. Medicine, Bronx, NY, 10461
Cancer Res; 41(11,part1):4637-4643 1981

We have developed a method for clonal growth of human mammary epithelial cells of both nonmalignant and malignant origin. Plating efficiencies of 1 to 50% were obtained by seeding second-passage mammary epithelial cells on fibroblast feeder layers in an enriched medium composed of various hormones and growth factors, as well as conditioned media from three specific human cell lines. Single mammary epithelial cells seeded sparsely onto the fibroblasts underwent at least eight population doublings to form large, readily visible colonies. Optimal colony formation required both feeder cells and the enriched medium. Epithelial colonies containing at least 16 cells were visible 5 days postseeding, and these colonies continued to grow progressively. Plating efficiency and colony size were similar on UV-irradiated or nonirradiated fibroblasts. The number of colonies formed was proportional to the number of epithelial cells plated. The colonies were identified as epithelial by the presence of human mammary epithelial antigens. (Author abstract) (31 Refs)

44. SECRETORY COMPONENT. A GLANDULAR EPITHELIAL CELL MARKER.

Harris JP, South MA
Div. Head and Neck Surgery, Dept. Surgery, Univ. California Medical Center, 225 Dickinson St., San Diego, CA, 92103
Am J Pathol; 105(1):47-53 1981

Secretory component (SC) has been demonstrated to be produced by both normal and malignantly transformed glandular epithelial cells. By an indirect immunofluorescent technique, this study surveys tumors of varied cellular origin in order to determine the reliability of SC as a marker for tumor cells derived from glandular epithelium. Both primary and metastatic tumors of glandular epithelial origin demonstrated SC fluorescence, while nonglandular epithelial tumors did not. This observation was extended to live single-cell preparations, which demonstrated intense cell-surface fluorescence only when glandular epithelial tumor cells were examined. Additionally, fixed, cytocentrifuged, single-cell preparations of glandular epithelial tumors demonstrated cytoplasmic SC fluorescence. When breast carcinoma was examined, all cases demonstrated SC, regardless of the degree of differentiation. This assay appears to have useful clinical application in that the findings of SC provides indication of the glandular epithelial origin of a malignantly transformed cell. (Author abstract) (13 Refs)

REVIEWS AND OTHER RELATED STUDIES

45. BREAST PATHOLOGY, EMPHASIZING PRECANCEROUS AND CANCER-ASSOCIATED LESIONS.

Jensen HM
Dept. Pathology, Sch. Medicine, Univ. California, Davis, CA, 95616
Comment Res Breast Dis; 2:41-86 1981

Present knowledge, ideas, and speculations about breast pathology are reviewed. Discussion of the normal female breast includes gross anatomy, microarchitecture, and histology of the pubertal, mature, and aging breast; biology of the nonpregnant mature female breast with consideration of the terminal ductal lobular unit and formation and reabsorption of secretions; normal variations and the undefinable border between normal and abnormal conditions; benign histopathological changes in an occasional lobular unit; and atypical changes. Benign breast disease is discussed, including changes in multiple lobular units resulting in a palpable mass, and papillomas in ducts proximal to terminal ducts. Changes signifying risk for subsequent invasive cancer, precancerous lesions, ductal carcinoma in situ, precancerous versus cancer-associated lesions, and lesions judged cancer-associated are discussed. Pathologic and clinical aspects of invasive cancer are described. Pathological clues that a breast is at risk for cancer are summarized. (17 Refs)

46. A FRESH APPROACH TO HUMAN BREAST CANCER.

Simpson HW, Mutch F, Giles C, Grant JK, Griffiths K, Halberg F, MacEwan J, McNicol AM, Turbitt M, Wilson D
Dept. Pathology, Royal Infirmary, Glasgow G4 02F, Scotland
Comment Res Breast Dis; 2:133-164 1981

Certain aspects of precancer breast biology are reviewed. From the epidemiologist's viewpoint the 'active' ovary plays a major role in mammary carcinogenesis. From the pathologist's viewpoint hyperplasia presents a risk state for neoplasia. A census of hyperplasia in pericancerous breast tissue from one infirmary is discussed and implications drawn. Terms are defined. Early attempts to measure the risk state by mammary thermal chronobiology are described. This method involves measuring surface temperatures on the breast, using thermistors or liquid crystal thermography. Results indicate that breast temperature fluctuates according to the menstrual cycle and also a daily cycle. The fluctuation appears to be at least partially controlled by hormonal variations. Abnormalities of the breast are accompanied by abnormal temperature variations. Further study may allow the use of thermography to detect precancerous conditions. (68 Refs)

47. NEOPLASIA AND HORMONAL CONTRACEPTION.

Huggins GR
Univ. Pennsylvania Sch. Medicine, Philadelphia, PA, 19104
Clin Obstet Gynecol; 24(3):903-925 1981

The relationships between use of oral contraceptives and neoplasia are reviewed. Problems of investigation include lack of suitable animal models, lag time following exposure to carcinogens before development of overt malignancy, low incidence of malignancies in young women, and the wide range of factors influencing neoplasia. Investigative methods include case reports, disease rates and trends, case comparisons, and cohort studies. Breast disease is discussed with respect to the preclinical phase of breast cancer, breast cancer and chronic mastitis, the estradiol hypothesis, and the relationships between oral contraceptive use and benign and malignant breast disease. The relationships of oral contraceptives to liver tumors, pituitary tumors, endometrial hyperplasia, cervical neoplasia, ovarian disease, and choriocarcinoma are evaluated based on current published data. (56 Refs)

48. BREAST CANCER SCREENING.

Milbrath JR, Moskowitz M, Bauermeister D
Breast Cancer Detection Unit, Medical Coll. Wisconsin, Milwaukee County Medical Complex, Milwaukee, WI

CRC Crit Rev Diagn Imaging; 16(3):181-218 1981

The current status of breast cancer screening is reviewed. The natural history of breast cancer is described, including high risk neoplastic changes, non-infiltrating carcinoma (including in situ ductal carcinoma and in situ lobular carcinoma), and infiltrating carcinoma. Histological types described include medullary, colloid, papillary, tubular, and adenoid cystic carcinomas, Paget's disease, and dermal carcinomatosis. Tumor differentiation by intramammary lymphatic extension, micrometastases to axillary lymph nodes, extranodal extension by metastatic carcinoma to axillary lymph nodes, and intramammary vascular invasion is discussed. A definition of screening, risk assessment and methods of detection (including physical examination, mammography, thermography, ultrasound, and computed tomography) are reviewed. Screening programs are summarized for the United States, the United Kingdom, Holland, Sweden, and Australia. Estimation of the benefit/risk ratio is detailed, using benefit models and risk estimates. (191 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. CHEMICAL COMPOUNDS AND CANCER RISK.
Schramm T, Janisch W
Zentralinstitut fur Krebsforschung der Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):561-565 1981
In GER

2. THE CARCINOGENICITY OF ARSENIC.
Pershagen G
Dept. Environmental Hygeine, Karolinska Inst., Stockholm, Sweden
Environ Health Perspect; 40:93-100 1981

3. THE CARCINOGENICITY OF CHROMIUM.
Norseth T
Inst. Occupational Health, Gydas vei 8, Oslo 3, Norway
Environ Health Perspect; 40:121-130 1981

4. ROLE OF COBALT, IRON, LEAD, MANGANESE, MERCURY, PLATINUM, SELENIUM, AND TITANIUM IN CARCINOGENESIS.
Kazantzis G
TUC Centenary Inst. Occupational Health, London Sch. Hygiene and Tropical Medicine, Keppel St., London WC1E 7HT, England
Environ Health Perspect; 40:143-161 1981

5. RECENT RESEARCH ON NICKEL CARCINOGENESIS.
Sunderman FW
Dept. Lab. Medicine, Univ. Connecticut Sch. Medicine, Farmington, CT, 06032
Environ Health Perspect; 40:131-141 1981

6. ROLE OF CADMIUM IN CARCINOGENESIS WITH SPECIAL REFERENCE TO CANCER OF THE PROSTATE.
Piscator M
Dept. Environmental Hygiene, Karolinska Inst., S-104 01 Stockholm, Sweden
Environ Health Perspect: 40:107-120 1981

7. CHELATING AGENTS IN BIOLOGICAL SYSTEMS.
Schubert J
Dept. Chemistry, Univ. Maryland Baltimore County, Catonsville, MD, 21228
Environ Health Perspect; 40:227-232 1981

8. BENZENE AS A RISK FACTOR.
Stobbe H
Universitatsklinik fur Innere Medizin 'Theodor Brugsch', Bereich Medizin der Humboldt-Universitat, Schumannstrasse 20/21, DDR-1040 Berlin, E. Germany
Arch Geschwulstforsch; 51(7):575-578 1981
In GER

9. FORMALDEHYDE IN DENTISTRY: A REVIEW OF MUTAGENIC AND CARCINOGENIC POTENTIAL.
Lewis BB, Chestner SB
800-A Fifth Ave., Suite 503, New York, NY, 10021
J Am Dent Assoc; 103(3):429-434 1981

10. CARCINOGENICITY OF HYDANTOINS: DATA, HYPOTHESES, AND PUBLIC REVIEWS.
Scoville B, White BG
Natl. Inst. Neurological and Communicative Disorders and Stroke, NIH, Bethesda, MD, 20205
Psychopharmacol Bull; 17(3):195-197 1981

11. PHENOXY ACIDS, CHLOROPHENOLS, AND CANCER.
Hardell L, Eriksson M
Onkologiska kliniken, Regionsjukhuset, Umea, Sweden
Lakartidningen; 78(34):2862-2863 1981
In SWE

12. PHENOXY ACIDS: A BRIEF REVIEW OF THE POSSIBLE HYGIENIC EFFECTS.
Edling C
Yrkesmedicinska kliniken, Regionsjukhuset, Linkoping, Sweden
Lakartidningen; 78(34):2861-2862 1981
In SWE

DIETARY FACTORS IN CARCINOGENESIS

13. NUTRITIONAL MODULATION OF CANCER.
Nauss KM, Newberne PM
Dept. Nutrition and Food Science, Massachusetts Inst. Technology, Cambridge, MA, 02139
Cancer Detect Prev; 3(2):367-417 1981

14. FIBER CARCINOGENESIS: EPIDEMIOLOGIC OBSERVATIONS AND THE STANTON HYPOTHESIS.
Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
JNCI; 67(5):977-989 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

15. EPIDEMIOLOGY.
Alderson MR
Dept. Epidemiology, Inst. Cancer Res., London, England
Recent Results Cancer Res; 78:1-19 1981

16. ATLAS OF CANCER MORTALITY IN THE PEOPLE'S REPUBLIC OF CHINA. AN AID FOR CANCER CONTROL AND RESEARCH.
Li JY, Liu BQ, Li GY, Chen ZJ, Sun XD, Rong SD
Dept. Cancer Epidemiology, Cancer Inst. Chinese Acad. Medical Sciences, 2, Yabao Lu, Chaoyang, Qu, Beijing, People's Republic of China
Int J Epidemiol; 10(2):127-133 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

17. SIXTH EAST GERMAN CANCER CONGRESS WITH INTERNATIONAL PARTICIPATION, BERLIN, MARCH 2-5, 1981.
Schramm T, Ebeling K, Schwarz R, Heise E, Glaser A, Tanneberger St, Anger G
No affiliation given
Arch Geschwulstforsch; 51(7):551-560 1981
In GER

18. EPIDEMIOLOGICAL STUDIES INTO THE POSSIBLE CARCINOGENICITY OF HAIR DYES.
Clemmesen J
(c/o P. Lohman), Medical Biological Lab. TNO., P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(1):65-79 1981

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

19. THE ROLE OF METALS IN CARCINOGENESIS: BIOCHEMISTRY AND METABOLISM.
Jennette KW
Dept. Chemistry, Dartmouth Coll., Hanover, NH, 03755
Environ Health Perspect; 40:233-252 1981

20. RECENT CONCEPTS OF INITIATION AND PROMOTION IN CARCINOGENESIS.
Becker FF
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Am J Pathol; 105(1):3-9 1981

21. ACTIVATED METABOLITES OF CARCINOGENIC HYDROCARBONS.
Harvey RG
Ben May Lab., Univ. Chicago, Chicago, IL, 60637
Acc Chem Res; 14(7):218-226 1981

22. RELATIONSHIP BETWEEN METAL TOXICITY TO SUBCELLULAR SYSTEMS AND THE CARCINOGENIC RESPONSE.
Squibb KS, Fowler BA
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Environ Health Perspect; 40:181-188 1981

23. ENZYMES INVOLVED IN THE REPAIR OF DAMAGED DNA.
Grossman L
Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 N. Wolfe St., Baltimore, MD, 21205
Arch Biochem Biophys; 211(2):511-522 1981

24. METAL-INDUCED INFIDELITY OF DNA SYNTHESIS.
Zakour RA, Kunkel TA, Loeb LA
Joseph Gottstein Memorial Cancer Res. Lab., Dept. Pathol., Univ. Washington, Seattle, WA, 98195
Environ Health Perspect; 40:197-205 1981

25. CHROMOSOME ABERRATIONS AND THEIR RELEVANCE TO METAL CARCINOGENESIS.
Vainio H, Sorsa M
Dept. Industrial Hygiene and Toxicology, Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Environ Health Perspect; 40:173-180 1981

MODIFICATION OF CARCINOGENESIS

26. METAL INTERACTIONS IN CARCINOGENESIS: ENHANCEMENT, INHIBITION.
Nordberg GF, Andersen O
Dept. Environmental Hygiene, Umea Univ., Umea, Sweden
Environ Health Perspect; 40:65-81 1981

27. EFFECT OF METALS ON MUTAGENESIS AND DNA REPAIR.
Rossman TG
Inst. Environmental Medicine, New York Univ. Sch. Medicine, 550 First Ave., New York, NY, 10016
Environ Health Perspect; 40:189-195 1981

METHODOLOGY IN CARCINOGENESIS RESEARCH

28. SISTER CHROMATID EXCHANGES: A REPORT OF THE GENE-TOX PROGRAM.
Latt SA, Allen J, Bloom SE, Carrano A, Falke E, Kram D, Schneider E, Schreck R, Tice R, Whitfield B, Wolff S
Harvard Medical Sch., Boston, MA, 02115
Mutat Res; 87(1):17-62 1981

29. EFFECTS OF METALS IN IN VITRO BIOASSAYS.
Sirover MA
Dept. Pharmacology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Environ Health Perspect; 40:163-172 1981

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MARCH, 1982

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PREVALENCE OF BREAST CANCER IN HUMAN POPULATIONS

1. MAMMARY GLAND CANCER. RETROSPECTIVE STUDY.

Vilchis Galindo BE
Centro Maternoinfantil 'Gral. Maximino Avila Camacho', Mexico, D. F., Mexico
Patol Quir Citol Exfoliativa; 7(1):19-24 1981

According to 1970 mortality data, in Mexico 8% of women died due to uterine cancer, and 3.9% due to mammary cancer (most were 45-49 yr old). Most common form of disease was the infiltrating intracanicular carcinoma. Mammary cancer was reviewed including: risks, clinical course, clinical stages, lymphatic nodes, metastases, different methods of diagnosis and treatment. (11 Refs) (In SPA)

2. CANCER AMONG THE FOREIGN-BORN IN NEW YORK STATE.

Nasca PC, Greenwald P, Burnett WS, Chorost S, Schmidt W
Bureau Cancer Control, New York State Dept. Health, Empire State Plaza, Albany, NY, 12237
Cancer; 48(10):2323-2328 1981

Cancer deaths among white, foreign-born residents of New York State (exclusive of New York City) during the yr 1969 through 1971 were analyzed according to country of birth. The largest numbers of immigrants came from Great Britain, Ireland, Germany, Austria, Poland, Italy, USSR, and Canada. Several distinctive features emerged from these data: Irish immigrants have an increased risk of dying from oropharyngeal, gastrointestinal, lung, and prostate cancers. Among all migrant groups studied, contrasting mortality patterns observed for carcinomas of the stomach, colon, and rectum provide further support for the concept that these neoplasms result from different etiologic processes. For the leukemias, lymphomas, and carcinomas of the breast and colon, each of the migrant groups acquired the higher risk common to others in the host country. This rise in risk suggests a major environmental component for cancers of these sites. (Author abstract) (15 Refs)

3. ADVANCES IN CANCER EPIDEMIOLOGY IN SOUTH AFRICA.

Harington JS
Cancer Res. Dept., Natl. Cancer Assoc. South Africa, P.O. Box 2000, Johannesburg 2000, South Africa
S Afr Cancer Bull; 25(1/2):9-18 1981

The epidemiology of cancer in South Africa (SA) is discussed through the review of four papers on the cancer pattern in black gold miners in SA (1964-79), comparison of cancer mortality rates in SA with those of other countries, cancer mortality rates for blacks, whites, coloreds, and Asians in SA (1970-77), and the cancer problem among blacks in SA. Mortality rates were compared for all groups (SA and US: United States). Much less cancer was found in the SA urban black than in any of the other groups. The SA colored community had rates which were very nearly the highest for most of the common cancers for each site of almost all the cancers considered. The cancer pattern in SA whites of both sexes was similar to that of US whites. Whereas US blacks had consistently higher rates than US whites but the same pattern, SA blacks had a different cancer pattern to that of either the coloreds or whites in SA. The pattern for SA blacks comprised high rates for esophagus, liver, and lung cancer in males, and for cervix and esophagus cancer in females, while rates for colorectum, stomach, and female breast cancer were low. Colored males had the highest cancer risk in SA. The colored female is not nearly as much at risk as the male. Comparison between SA colored and US black males showed cancer rates to be higher in the coloreds. The overall mortality rate for cancer in SA urban blacks was lower than that for SA whites or coloreds, both males and females. The implications of these studies are discussed. (17 Refs)

4. CANCER INCIDENCE IN THE NETHERLANDS ANTILLES: A SURVEY COVERING THE PERIOD 1968-1979.

Freni SC, Freni-Titulaer LW
Dept. Pathology, Landslaboratorium, 55 Heelsumstraat, Curacao, Netherlands Antilles, West Indies
Cancer; 48(11):2535-2541 1981

In 1977 a retrospective study was started into the cancer incidence in the Netherlands Antilles, simultaneously with the onset of a cancer registry. This paper presents the results of this study and of the running registry, together covering a period of 12 yr. In total, 1,496 cancer cases were registered in males, and 1,480 in females. The resulting age-standardized cancer rate (World Standard Population) was 215 cases per 100,000 males and 164 cases per 100,000 females. The most frequently involved primary sites in males were, in order of frequency, lung, stomach, prostate, skin, and esophagus. Cancer in females was most frequently found in breast, uterine cervix, skin, stomach and esophagus. A comparison is made with countries inside and outside the Caribbean region, and a short comment is made on possible etiologic factors. (Author abstract) (17 Refs)

5. CANCER DEATHS BY CITY AND COUNTY IN JAPAN (1969-1971): A TEST OF SIGNIFICANCE FOR GEOGRAPHIC CLUSTERS OF DISEASE.

Ohno Y, Aoki K
Dept. Preventive Medicine, Nagoya Univ. Sch. Medicine, Nagoya, Japan
Soc Sci Med [Med Geogr]; 15(1):251-258 1981

The geographic distribution of esophageal, breast, and uterine cancer mortality by city and county in Japan was analyzed by a chi-square significance test. The test procedure included identification of all geographically adjacent areas, enumeration of observed adjacent concordant category pairs (accp), and calculation of expected accp. Areas with high esophageal cancer mortality were significantly clustered in both sexes, and those with low mortality were clustered in males. In the case of uterine cancer, significant aggregations were observed in areas with low or slightly high mortality rates. There was no significant aggregation for breast cancer. The validity of the chi-square test was confirmed by a Monte Carlo approach to Knox's test for space-time clustering. (11 Refs)

6. INTERNATIONAL COMPARISON OF TRENDS IN CANCER MORTALITY FOR SELECTED SITES.

Hayakawa N, Kurihara M
Dept. Epidemiology and Social Sciences, Res. Inst. Nuclear Medicine and Biology, Hiroshima, Japan
Soc Sci Med [Med Geogr]; 15(1):245-249 1981

Trends in mortality rates due to cancer based on age adjusted death rates in 23 countries are reported to help elucidate causal factors. Annual variation in rates from 1954 to 1975 were calculated under the assumption that the mortality rates changed exponentially and the number of deaths followed the Poisson distribution. Results for males showed significant increases in 22 countries. Sites showing greatest increases were respiratory organs (5.9% to 0.9%) and intestine (3.9% to-4.0%). Results for females showed significant decreases. Sites with increased incidence of cancer included breast (1.8% to 0.2%) and intestine (4.1% to-0.7%), while uterine (-0.6% to-3.8%) and stomach (0.3% to-4.8%) cancers decreased. Specific countries showing large increases include Portugal with 0.3% to 0.8% increase in stomach cancer, and Italy with a significant increase in cancer of all sites except stomach. The 23 countries investigated are 'developed' countries; cancer death rates need to be studied in developing countries as well. (10 Refs)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

7. INDEPENDENT RISK FACTORS OF BENIGN AND MALIGNANT BREAST LESIONS.

Soini I, Aine R, Lauslahti K, Hakama M
Dept. Public Health, Univ. Tampere, Box 607, 33101 Tampere 10, Finland
Am J Epidemiol; 114(4):507-514 1981

The purpose of this study is to evaluate the risk factors of benign breast disease and to compare them with the known risk factors of breast cancer in order to make inferences on the relationship between benign breast disease and breast cancer. All benign breast lesions diagnosed from the population of the city of Tampere, Finland in 1974-1977 were reclassified by two pathologists into two groups of dysplasia and two groups of tumors. In the risk analysis of 422 age-matched pairs no group of benign lesions had risk factors consistently similar to those of breast cancer. it is therefore likely that either benign breast disease is not associated with breast cancer or it is an independent risk factor, not associated with the other high risk indicators of breast cancer. (Author abstract) (34 Refs)

8. BODY WEIGHT AND PROGNOSIS IN BREAST CANCER.

Boyd NF, Campbell JE, Germanson T, Thomson DB, Sutherland DJ, Meakin JW
Dept, Medicine, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario, M4X 1K9, Canada
JNCI; 67(4):785-789 1981

We have examined the relationship between risk factors for breast cancer incidence and the subsequent prognosis of breast cancer among patients in a randomized controlled trial of adjuvant ovarian ablation. Body wt was the only risk factor found to be associated with statistically significant differences in survival. This finding could not be explained by a disproportionate number of anatomically more advanced tumors in the heavier women. In premenopausal women aged 45 yr or more, the only group to benefit from adjuvant ovarian ablation, there was an interaction of treatment and wt, suggesting that wt exerts its influence on prognosis by a hormonal mechanism. The prognostic effect of wt was generally most marked in patients with tumors whose prognostic characteristics were favorable, and in these patients wt loss as an adjuvant treatment may reduce the frequency of disease recurrence. (Author abstract) (22 Refs)

9. COFFEE AND TEA CONSUMPTION AND BREAST DISEASE.

Lawson DH, Jick H, Rothman KJ
(c/o Jick), Boston Collaborative Drug Surveillance Program, 400-1 Totten Pond Rd., Waltham, MA, 02154
Surgery; 90(5):801-803 1981

The relation of coffee and tea consumption to fibrocystic disease of the breast and to breast cancer was studied in 451 women hospitalized for these diseases and interviewed since 1972. We found a modest, positive association between hot beverage consumption and both diseases. However, there was no apparent dose-response effect. These data add little support to the hypothesis that methylxanthine consumption plays an etiologic role in the development of fibrocystic or malignant disease of the breast. (Author abstract) (5 Refs)

10. NUTRIENT INTAKES IN RELATION TO CANCER INCIDENCE IN HAWAII.

Kolonel LN, Hankin JH, Lee J, Chu SY, Nomura AM, Hinds MW
Epidemiology Program, Cancer Center Hawaii, Univ. Hawaii, Honolulu, HI, 96813
Br J Cancer; 44(3):332-339 1981

A representative sample of 4,657 adults greater than or equal to 45 yr of age from the five main ethnic groups in Hawaii (Caucasians, Japanese, Chinese, Filipinos and Hawaiians) were interviewed during 1977-1979 regarding their diets. Quantitative food-consumption histories were obtained, from which av daily intakes of fat (saturated, unsaturated, cholesterol, meat, dairy, fish, animal, vegetable and total), protein (animal, meat, fish, dairy and total), carbohydrate, and vitamins A and C (including supplements) were calculated using food-consumption data from standard sources. Multiple regression analysis, with sex as a controlled variable, was used to assess the statistical relationship between these ethnic-sex-specific intakes and corresponding population-based cancer incidence rates of 15 selected sites for which nutrient components are suspected to be either causal or protective. Based on pre-set criteria for establishing important relationships, significant positive associations were found for 6 of the cancer sites: breast cancer with fat (saturated, unsaturated, animal, total) and protein (animal), corpus-uteri cancer with the same components as breast cancer, prostate cancer with fat (saturated, animal) and protein (animal, total), stomach cancer with fat (fish only) and protein (fish only), lung cancer with cholesterol, and laryn geal cancer with cholesterol. Breast and corpus-uteri cancers also showed significant negative associations with carbohydrate intake. The implications of these findings for future research are discussed. (Author abstract) (32 Refs)

11. DIET AND REPRODUCTIVE HORMONES: A STUDY OF VEGETARIAN AND NONVEGETARIAN POSTMENOPAUSAL WOMEN.

Armstrong BK, Brown JB, Clarke HT, Crooke DK, Hahnel R, Masarei JR, Ratajczak T
Unit Epidemiology and Preventive Medicine, Univ. of Western Australia, Nedlands 6009, Western Australia
JNCI; 67(4):761-767 1981

In comparison with matched nonvegetarian women, postmenopausal vegetarian women were found to have lower urinary levels of estriol and total estrogens, lower plasma prolactin levels, and higher plasma sex hormone-binding globulin (SHBG) levels. These differences were not explained by differences in body wt or obesity. Plasma SHBG levels were highly correlated with plasma high-density lipoprotein cholesterol levels, which were also higher in vegetarians than in non-vegetarians. These hormonal differences may explain the lower rates of endometrial and possibly breast cancer that have been observed previously in vegetarian women. (Author abstract) (37 Refs)

12. PROPORTIONATE MORTALITY STUDY OF FUR DYERS (MEETING ABSTRACT).

Haring MK, Waxweiler RJ, Walrath J

National Institute for Occupational Safety and Health, Cincinnati, OH

Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

In recent studies, numerous constituents of oxidative hair dyes were shown to be mutagenic by the Ames test; some were also proven to be carcinogenic, inducing tumors of the liver, lymphatic system or other sites, in laboratory animals. Epidemiologic studies have associated exposure to hair dyes with increased risks of breast, cervical and lung cancers and chromosomal damage among hairdressers and consumers. During the past century, fur dyers have used oxidative dyes extensively to tint and color animal fur. To investigate the health effects of long term exposures to oxidative dyes, a retrospective cohort mortality study is being conducted on 980 fur dyers and processors of the Fur, Leather and Machinists Workers Union who were pensioned between 1952 and 1977. The standardized mortality ratio (SMR), using age-sex-race, calendar time, and cause-specific mortality rates for United States, will be calculated for all causes of death including all malignant neoplasms. In addition to oxidative dyes, other possible occupational exposures are saw dust, used to absorb excess dye from furs, and formaldehyde. Analyses of job classifications and ethnic origins also will be conducted. (no Refs)

13. TORRE-MUIR SYNDROME: SEBACEOUS GLAND NEOPLASIAS, KERATOACANTHOMAS, MULTIPLE INTERNAL CARCINOMAS, AND HEREDITY.

Worret WI, Burgdorf WH, Fahmy A, Pitha J

(c/o Burgdorf) 619 N. E. 13th, Oklahoma City, OK, 73104

Hautarzt; 32(10):519-524 1981

Three cases of Torre-Muir syndrome (TM) are reported. Characteristic of TM are sebaceous gland neoplasia or acanthoma (often multiple), multiple primary carcinoma of various internal organs, and a hereditary factor (possibly autosomal dominant). Cases included two men and one woman, aged 47-64 yr, all Caucasians. All three had a family history of cancer among maternal grandparents and their descendents. Diseases occurring among relatives included renal carcinoma, colon carcinoma, breast cancer, leukemia, bone cancer, ovarian tumor, and skin tumors. Nine male and ten female relatives of the three patients developed internal malignancies. One male and one female developed skin malignancies. Intestinal polyposis occurred in two male relatives. TM apparently is linked to family cancer syndrome. (35 Refs) (In GER)

POSSIBLE IATROGENIC FACTORS IN HUMAN BREAST CARCINOGENESIS

14. CONJUGATED ESTROGENS AND BREAST CANCER RISK IN WOMEN.

Hoover R, Glass A, Finkle WD, Azevedo D, Milne K

Environmental Epidemiology Branch, Div. Cancer Cause and Prevention, NCI, NIH, Public Health Service, U.S. Dept. Health and Human Services, Bethesda, MD, 20205

JNCI; 67(4):815-820 1981

The relationship between conjugated estrogen(s) (CE) and breast cancer was investigated by the examination of the records of 345 women with newly diagnosed breast cancer and 611 healthy controls belonging to a prepaid health plan. Use of CE was associated with a 40% elevation in risk [relative risk (RR) = 1.4; 95% confidence interval = 1.0-2.0]. The RR was 1.3 for menopausal women with intact ovaries and 1.5 for those with ovaries removed. There was statistically significant evidence of a dose-response relationship with the three measures of dose evaluated. RR's rose to about twofold for women with 10 or more CE prescriptions noted in their charts, for those with 5 yr or more between their first and last prescription, and for those with a usual daily dose of 1.25 mg or more. The RR associated with having ever used CE and with long-term use was highest among those women with a family history of breast cancer. These data support the hypothesis that long-term use of CE is associated with increased breast cancer risk. (Author abstract) (41 Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

15. A TWO-YEAR STUDY WITH CIMETIDINE IN THE RAT: ASSESSMENT FOR CHRONIC TOXICITY AND CARCINOGENICITY.

Leslie GB, Noakes DN, Pollitt FD, Roe FJ, Walker TF

Smith Kline and French Res. Ltd., Welwyn Garden City, Hertfordshire, England

Toxicol Appl Pharmacol; 61(1):119-137 1981

Potential carcinogenic activity of cimetidine (gastric acid secretion inhibitor) was studied in ICI Wistar-derived rats. Rats were given cimetidine by gavage at 950, 378, and 150 mg/kg/day for 2 yr. Cimetidine treatment did not affect food consumption, body wt gain, survival, or hematological indices. Hemorrhagic lungs and increased liver wt were recorded in rats from higher dose groups. An overall tumor incidence in cimetidine-treated groups did not differ significantly from that in controls. Significantly increased incidence of Leydig-cell tumors was recorded in rats killed during wk 105 and 106; the increase was not dose-related. Cimetidine did not affect the incidence of mammary gland neoplasms. (9 Refs)

16. EXPERIMENTAL LESIONS INDUCED IN RATS BY POLYVINYL CHLORIDE (PVC) COMBUSTION FUMES.

Dessy E, Faa G, Calatri S, Bucarelli A

II Cattedra di Anatomia e Istologia Patologica, Universita di Cagliari, Cagliari, Italy

Boll Soc Ital Biol Sper; 57(11):1278-1281 1981

The effect of pure polyvinyl chloride (PVC) powder combustion fumes was studied in 14 adult white Wistar rats.

Forced inhalation of wood combustion fumes was given to eight control rats. The forced inhalation was administered for 1 hr every day during 30-180 days. The rats were sacrificed approx 1 yr after the end of the experiment. While they were exposed to fumes animals were irritable, aggressive, dehydrated, and lost wt. Most significant histological findings were in lung (metaplasia of bronchial epithelium), and liver (enlargement of sinusoidal bed, and activation of Kupffer cells). Animals treated for an extended period of time had marked alopecia of the neck and back, and histologically sebaceous gland hyperplasia. Two rats had three sc tumors, histologically diagnosed as adenocarcinomas (neck, and mammary sites). (7 Refs) (In ITA).

17. GROSS AND HISTOPATHOLOGIC EFFECTS OF MEDROXYPROGESTERONE ACETATE AND PROGESTERONE ON THE MAMMARY GLANDS OF ADULT BEAGLE BITCHES.

Concannon PW, Spraker TR, Casey HW, Hansel W
Dept. Physiology, Cornell Univ., 820 Veterinary Res. Tower, Ithaca, NY, 14853
Fertil Steril; 36(3):373-387 1981

Medroxyprogesterone acetate (MPA: 0.2-75 mg/kg, im, every 3 mo for 1-1.5 yr) was administered to intact, ovariectomized, or hypophysectomized beagles in groups of 6-12 animals each. Intact, noncycling controls received progesterone implants (3-22 cm/kg). MPA equal or greater than 2.0 mg/kg completely suppressed ovulatory cycles, and the suppression was associated with the maintenance of elevated MPA serum levels. MPA treatment (10 and 75 mg/kg) resulted in an increased incidence of multiple, large mammary gland nodules (5-11 mm). These nodular lesions consisted of simple or complex lobular hyperplasia, simple or complex adenomas, and benign mixed tumors; no malignant tumors were found. The nodules occurred after 4-6 of treatment in older dogs and after 8-15 mo in young dogs. Ovariectomy did not affect tumor induction by 75 mg/kg MPA, but adenoma incidence was significantly lower in hypophysectomized than in intact dogs. Low progesterone doses prevented ovarian cycles and higher doses resulted in some degree of mammary enlargement, glandular activity, and nodular development. (29 Refs)

18. AGE-SPECIFIC INCIDENCE OF NEOPLASMS IN UNTREATED NZR/GD RATS: AN INBRED STRAIN WITH CARDIOVASCULAR TUMOURS AND LIVER GLYCOGEN STORAGE DISEASE.

Goodall CM, Doesburg RM
Hugh Adam Cancer Biology Res. Unit., Dept. Surgery, Univ. Otago, Dunedin, New Zealand
J Pathol; 135(2):149-157 1981

Age-specific incidence of neoplasms in 650 untreated NZR rats was examined. The most common tumors were pituitary adenomas (76/126 of the tumor bearing female rats), lung adenomas (33/126 females), breast tumors (24/126 females), liver tumors (11/126), and cervix fibromas (11/126). Among 81 tumor bearing males, atriocaval mesotheliomas were found in 37 animals and lung adenomas in 32. For the first 1.5 yr of life, survival curves for males and females were indistinguishable, but after 550 days the age-specific mortality was consistently higher in males. No statistically significant difference in overall survival was found. Results support the theory that atrial-caval tumors arise from a developmental anomaly and are capable of invading adjacent tumors and metastasizing. Evidence of metastasis was found in 11 cases (3 females and 8 males). (23 Refs)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

19. MAMMARY-TUMOUR INCIDENCE IN SPRAGUE-DAWLEY RATS TREATED WITH 7,12-DIMETHYLBENZ(A)ANTHRACENE: EFFECT OF PREGNANCY AND LACK OF EFFECT OF UNILATERAL LACTATION.

Moore BP, Hayden TJ, Forsyth IA
Sch. Pathology, Middlesex Hosp. Medical Sch., London W1P 7LD, England
Br J Cancer; 44(3):451-455 1981

Mammary teat removal (thelectomy) was performed unilaterally in female Sprague-Dawley rats at 35 days of age. They were given 7,12-dimethylbenz(a)anthracene (DMBA) when aged either 55 days or 79 days. One third were unmated; one third were mated 1 wk and one third mated more than 3 wk after DMBA administration. Animals were killed when tumor-positive or after 1 yr, when mammary lesions had developed in 99% of rats. The mean latent period for adenocarcinomas was 18.9 +-2.0 wk. Benign mammary tumors, mainly secretory adenomas, developed significantly later (39.2 +-1.7 wk). The rapid unilateral involution of the thelectomized glands at parturition had no effect on the localization of either adenocarcinomas or benign mammary tumors. Pregnancy and delayed DMBA administration markedly reduced the incidence of adenocarcinomas; lactation had no significant effect. In a separate experiment, precocious puberty induced with pregnant-mare-serum gonadotrophin in 30-day-old female Sprague-Dawley rats enabled their first pregnancy and lactation to be completed by 80 days of age. Parity before carcinogen administration significantly delayed the development of adenocarcinomas. (Author abstract) (19 Refs)

20. RELATION BETWEEN ADRENAL FUNCTION AND 7,12-DIMETHYLBENZ[A]-ANTHRACENE-INDUCED MAMMARY CANCER OF THE RAT.

Nakamura Y, Kodama M, Kodama T
Dept. Surgery, Inst. Balneotherapeutics, Kyushu Univ., 4546 Tsurumihara, Beppu 874, Japan
Gan; 72(5):679-683 1981

The excretions of urinary steroids were investigated in rats in the course of mammary carcinogenesis by 7,12-dimethylbenz[a]anthracene (DMBA). The carcinogen was fed to female Sprague-Dawley rats on days 50 and 64 after birth at a dose of 10 mg each. The excretion of urinary androgen, 11-deoxy-17-oxosteroid (11-DOOS), increased temporarily (at 80 days of age) in DMBA-treated rats as compared with non-treated controls. The excretion of adrenal corticosteroid, 17-deoxy-corticosteroid (17-DOCS), was lower than normal in the rats that failed to develop tumors within 200 days after receiving DMBA. The difference between the above non-responders and the tumor-developing responders (or the non-treated controls) was significant at 80 and 120 days of age, but not at 160 days of age. The final tumors wt at 160 days of age were also positively correlated to the excretion of 17-DOCS at 130 days of age. It was indicated that the overall process of DMBA carcinogenesis could be promoted by the endogenous adrenocortical steroids. The possible mechanism underlying the production of mammary cancer is discussed in the light of the metabolic intimacy between DMBA and the adrenal steroids. (Author abstract) (17 Refs)

21. EFFECT OF AGE AT START OF DIETHYLSTILBESTROL (DES) TREATMENT ON MAMMARY TUMOR INDUCTION IN C3H MICE (MEETING ABSTRACT).

Greenman DL, Cameron A, Highman B, Frith CH, Norvell MJ
National Center of Toxicology Research, Jefferson, AR
Toxicologist; 1(1):155 1981

To determine the effect of age at the start of DES administration, C3H/HeN female mice with a high (MTV+) and low (MTV-) titer of murine mammary tumor virus were continuously fed a diet containing 640 ppb DES. MTV+ mice were started on DES at ages 21, 35, 49, or 77 days (d) and MTV- mice at 21, 35, 49, or 63 d. Mammary tumors were detected by palpation and mice were removed from experiment when tumor reached a diameter of 1 cm. Time-to-tumor data are based on time of removal with a histologically verified mammary tumor. DES induced only mammary tumors in MTV+ mice. In the longer-lived MTV- females, DES induced mammary tumors and a low frequency of pituitary adenomas, uterine adenocarcinomas and mesotheliomas. The DES starting age affected only mammary tumor induction. In MTV+ mice, the percentages of the starting populations that developed mammary tumors (frequency) were 86% for controls, 88% for mice started at 49 or 77 d and 98% for mice started at 21 or 35 d. The times till half of the starting populations had tumors (t50) were 265 d for controls, 190 d for the 49 and 77 d mice, and 160 d for mice started at 21 or 35 d. In MTV- females, frequencies were 2% for controls and 50%, 80%, or 88% for mice started at 49 or 63 d, 35 d, and 21 d respectively. For these latter 3 groups, t50s were 850, 500, and 385 d, respectively. Age at the start of treatment strongly influenced the effect of DES on mammary tumor frequency and time-to-tumor in C3H (MTV-) but had less effect in MTV+ mice. These findings point out the important role age at the initiation of treatment may have in evaluating the potential toxicity of a test compound. (no Refs)

22. CHEMOPREVENTION OF MAMMARY TUMORIGENESIS BY A COMBINED REGIMEN OF SELENIUM AND VITAMIN A.

Ip C, Ip MM
Dept. Breast Surgery, Roswell Park Memorial Inst., Buffalo, NY, 14263
Carcinogenesis; 2(9):915-918 1981

The effect of combined administration of selenium (Se) and retinyl acetate (RA) was studied in female Sprague-Dawley rats with 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary gland tumors. DMBA was given intragastrically at 5 mg/wk for 3 wk. Starting 2 wk before initiation of DMBA administration, rats were fed a diet supplemented by Se (4 mg/kg) and/or RA (250 mg/kg) for 26 wk. Incidence of mammary gland tumors in rats exposed to DMBA alone was 90.0%, compared with 53.3% in rats treated with Se alone, 46.7% in rats treated with RA alone, 16.6% in rats treated with Se + RA for 28 wk, and 50.0% in rats treated with Se + RA-supplemented diet for only 18 wk. (32 Refs)

23. ENHANCEMENT BY RETINYL ACETATE OF HORMONE-INDUCED MAMMARY TUMORIGENESIS IN FEMALE GR/A MICE.

Welsch CW, Goodrich-Smith M, Brown CK, Crowe N
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
JNCI; 67(4):935-938 1981

Feeding of retinyl acetate (82 mg/kg ration) for 13-16 wk to estrone- and progesterone-treated nulliparous and multiparous inbred GR/A mice resulted in a substantial increase in the incidence of mammary carcinomas. Mammary carcinoma incidence in nulliparous control and retinoid-fed mice in experiment 1 was 22/65 (34%) and 37/65 (57%) (p less than 0.05), respectively; in experiment 2, 27/48 (56%) and 37/48 (77%) (p less than 0.05), respectively. Mammary carcinoma incidence in multiparous control and retinoid-fed mice in experiment 1 was 13/30 (43%) and 23/30 (77%) (p less than 0.05), respectively; in experiment 2, 19/19 (100%) and 19/19 (100%), respectively. The purported chemopreventive activities of retinyl acetate in murine mammary tumorigenesis were not demonstrated in this study; indeed, the vitamin A analog appeared to enhance this oncogenic process in the steroid hormone-treated GR mouse mammary cancer model. (Author abstract) (25 Refs)

24. INHIBITORY EFFECT OF HUMAN URINARY EXTRACT ON THE GROWTH OF DMBA-INDUCED MAMMARY TUMORS IN HOLTZMAN RAT.

Sarkar S, Shah PN, Bagli NP
Cancer Res. Inst., Bombay 400 012, India
Neoplasma; 28(4):457-461 1981

The effect of a crude protein fraction from human urine having gonadotropin inhibitory activity (CGIM) was observed on the growth of 7,12-dimethylbenz(a)anthracene induced mammary tumors in the Holtzman rat. Results show that while in 12 out of 13 tumors, tumor growth was retarded/regressed following 2-4 wk of CGIM treatment, tumor growth in control rats was unabated. However, no positive correlation with hormone dependency and tumor regression could be established. Further, this crude anti LH material was found to be non-toxic to tumor cells in vitro. (Author abstract) (11 Refs)

25. INHIBITORY ACTION OF ASPARAGUS RACEMOSUS ON DMBA-INDUCED MAMMARY CARCINOGENESIS IN RATS.

Rao AR
Cancer Biology Lab., Sch. Life Sci., Jawaharlal Nehru Univ., New Delhi-110 067, India
Int J Cancer; 28(5):607-610 1981

The present paper reports the inhibitory effect of Asparagus racemosus on DMBA-induced mammary tumorigenesis in rats of Holtzman strain. When virgin female rats, normal or primed with 17-beta-estradiol treatment, are put on diets containing 0.25%, 0.5%, 1% or 2% Asparagus root extract powder prior to their exposure to DMBA, mammary tumor incidence shows a sharp decline. (Author abstract) (39 Refs)

26. THE BINDING OF 7,12-DIMETHYLBENZ[A]ANTHRACENE TO MAMMARY GLAND MACROMOLECULES IN THE HAMSTER: EFFECTS OF ENOVID FEEDING OR TRANSPLACENTAL EXPOSURE TO DIETHYLSTILBOESTROL.

Hertzog PJ, Lawson TA, Gingell R
Cancer Res. Unit, Univ. York, Heslington, York YO1 5DD, England
Chem Biol Interact; 37(1):199-205 1981

The covalent binding of 7,12-[3H]dimethylbenz[a]anthracene ([3H]DMBA) to mammary gland macromolecules was studied in hamsters fed a contraceptive mixture, Enovid, those exposed transplacentally to diethylstilbestrol (DES), and controls. Compared with rats, hamsters are relatively resistant to DMBA mammary carcinogenesis, but susceptibility is increased by either of the above treatments with Enovid or DES. The amount of DMBA bound to DNA and protein was 4-5x greater than to RNA, but only DNA binding was persistent. Fifty-three percent of the DNA-bound DMBA was still present after 8 days. The amount of DMBA bound to hamster mammary DNA and its persistence was similar to that found in rats. Neither Enovid nor DES treatment altered the levels of binding to mammary macromolecules, nor their persistence. These results indicate that the species differences in the susceptibility to DMBA-induced mammary carcinogenesis in hamsters and rats, and modification of the former by hormones, is not due to differences in the activation of carcinogens. The role of hormones such as prolactin in the promotion phase of mammary gland carcinogenesis may explain these differences. (Author abstract) (18 Refs)

27. INFLUENCE OF GLAND DIFFERENTIATION ON BINDING OF 7,12-DIMETHYLBENZ(A)-ANTHRACENE (DMBA) TO DNA OF HUMAN BREAST EPITHELIAL CELLS IN PRIMARY CULTURE (MEETING ABSTRACT).

Tay LK, Russo IH, Miller J, Russo J
Department of Biology, Michigan Cancer Foundation, Detroit, MI, 48201
In Vitro; 17(3):201 1981

DMBA-induced rat mammary gland carcinogenesis depends upon binding of DMBA to DNA. Both the incidence of carcinomas and binding of DMBA to DNA are inversely related with age of the animal and degree of gland differentiation. To determine if DMBA binds to human breast epithelial cells and whether this binding is also influenced by patient's age and gland differentiation, the present study was carried out. Normal human breast tissues were obtained from patients ranging in age from 20 to 60 yr. Primary epithelial cell aggregates were prepared from these tissues and after 4 days in culture were treated with 3H-DMBA. The amount of binding of DMBA to DNA was not related to the age of patient, but was related to the type of structures present in the gland: higher binding was obtained in cultures from more undifferentiated breasts (few lobules) or breasts with ductal hyperplasia; lowest binding was obtained in cultures from well-differentiated post-lactational glands (abundant lobular formation. These results indicate that human mammary epithelial cells possess the ability to metabolize DMBA to products that react with DNA, and further show that binding of DMBA to DNA is dependent on the degree of differentiation of the mammary gland. (no Refs)

28. METABOLISM OF BENZO[A]PYRENE BY HUMAN MAMMARY EPITHELIAL CELLS: TOXICITY AND DNA ADDUCT FORMATION.

Stampfer MR, Bartholomew JC, Smith HS, Bartley JC
(c/o Bartley) Peralta Cancer Res. Inst., Peralta Hosp., 3023 Summit St., Oakland, CA, 94609
Proc Natl Acad Sci USA; 78(10):6251-6255 1981

Pure cultures of human breast epithelial cells and of fibroblastic cells in early passage provided the opportunity to ask whether either cell type had the capability for metabolizing chemical carcinogens and, if so, was the fate of the metabolic products compatible with chemical carcinogens being a factor in the initiation of breast cancer in women. For this purpose, cells were exposed to benzo[a]pyrene (BaP), and (i) the influence on growth potential and (ii) the extent, type, and persistence of adducts between the metabolites of BaP and DNA were measured. Compared with fibroblasts, inhibition of growth by epithelial cells was 50-100x more sensitive to BaP. Because of this differential sensitivity, epithelial cells were exposed to 4.0 uM BaP and fibroblasts were exposed to 4.0 uM BaP in the studies of DNA adduct formation. Separation by high-pressure liquid chromatography of adducts between (+-)-7,8-dihydroxy-9,10-expoxy-7,8,9,10 tetrahydrobenzo[a]pyrene (BaP diol epoxide) and nucleosides from purified DNA revealed that epithelial cells contained modified DNA within 6 hr after adding BaP. Adducts between the 7R anti stereoisomer of BaP diol epoxide and deoxyguanosine predominated at all times. syn BaP diol epoxide adducts with deoxyguanosine and what appeared to be BaP diol epoxide adducts with deoxycytidine were consistently present but at much lower frequency. All three types of BaP diol epoxide-DNA adducts persisted in epithelial cells for 72 hr in BaP-free medium. No adducts were detected in fibroblastic cultures until 96 hr after first exposure to BaP. At this time, the type and extent of BaP diol expoxide-DNA adduct formation was similar to that in epithelial cells exposed to one-tenth the dose of BaP. The type, extent, rate of formation, and persistence of the adducts in human breast epithelial cells was similar to that in cells transformable by exposure to BaP, an indication that they may be targets for chemically induced carcinogenesis. (Author abstract) (42 Refs)

29. CARCINOGENICITY OF INHALED 1,2-DIBROMOETHANE IN RATS TREATED WITH DISULFIRAM (MEETING ABSTRACT).

Wong LC, Winston JM, Hong CB
Midwest Research Institute, Kansas City, MO
Toxicologist; 1(1):130 1981

A chronic inhalation study of ethylene dibromide (EDB) was conducted in Sprague Dawley rats. The study consisted of four groups of rats receiving control air and control diet, 20 ppm of EDB and control diet, control air and 0.05% of disulfiram (DS) in the diet, and 20 ppm of EDB and 0.05% of DS in the diet, over a period of 18 mo. Rats receiving 20 ppm of EDB showed high mortality and an increase in tumor incidences in mammary glands, spleen, adrenals, liver, kidneys, and sc tissues. A combination of 20 ppm of EDB and 0.05% DS in the diet caused earlier deaths and high mortality rate, decreases in body wt gain, food consumption, Hb, hematocrit and RBC counts in rats. This combination of EDB and DS treatment also caused early development and high incidences of tumors in liver, spleen, kidneys, adrenals, thyroids, lungs, mesentary and mammary tumors. In addition, 90% of male rats that received a combination of EDB and DS treatment had testicular atrophy. Addition of DS treatment caused early deaths and high mortality rate, and promoted not only the tumor incidences in various organs and tissues in both male and female rats, but also the testicular atrophy in rats. (no Refs)

30. EFFECT OF 3,5,3'-TRIIODO-L-THYRONINE ON THE INCIDENCE AND GROWTH KINETICS OF SPONTANEOUS MAMMARY TUMORS IN C3H/HEN MICE.

Sellitti DF, Tseng YC, Latham KR
Dept. Medicine, Uniformed Services Univ. Health Sciences, Bethesda, MD, 20014
Cancer Res; 41(12):5015-5019 1981

The present study compares the incidence and growth kinetics of spontaneous mammary tumors in 3,5,3'-triiodo-L-thyronine (T3)-treated (0.7 ug/day, ip) C3H/HeN retired breeder mice with tumors occurring spontaneously in this strain (0.15 M NaCl, ip). T3 treatment markedly increased the rate of tumor incidence but had no effect on tumor growth rate as measured by tumor doubling time. A comparison of tumor labeling index and mitotic index between the two groups showed no difference. A histological comparison of the mammary glands in the two groups showed no significant difference in number of hyperplastic alveolar nodules. However, ductal-alveolar development was more pronounced in the 0.15 M NaCl-treated control group; consistent with this observation was the finding of lower levels of serum prolactin in the T3-treated group. Since mammary tumorigenesis was increased in T3-treated mice in spite of lower levels of serum prolactin, a well-known promoter of spontaneous mammary tumor in mice, a direct role for T3 in the process of tumor formation is suggested. (Author abstract) (45 Refs)

31. PEROXIDASE ACTIVATION OF N-OH-AAF BY RAT MAMMARY GLAND PARENCHYMAL CELLS (MEETING ABSTRACT).

Wong PK, Hampton MJ, Floyd RA
Oklahoma Medical Research Foundation, Oklahoma City, OK
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Rat mammary gland parenchymal cells activate N-hydroxy-2-acetylaminofluorene (N-OH-AAF) to 2-nitrosofluorene (NOF) and N-acetoxy-2-acetylaminofluorene (N-OAC-AAF) via a nitroxyl free radical form of the carcinogen. Prostaglandin synthetase has a peroxidase activity and hence we have examined parenchymal cells to determine if the activation of N-OH-AAF in the cells occurs by this route. Freshly isolated cells activate N-OH-AAF to NOF as detected by high pressure liquid chromatography (HPLC). Cells frozen at-60C are more active. N-OH-AAF activation appears to be peroxidative since ascorbate and p-aminophenol completely inhibit NOF formation. Neither the acyl-transferase nor deacylase route occurs to any appreciable extent in the cells. Exogenously added arachidonate enhances N-OH-AAF activation and the inhibitor 5,8,11,14-eicosatetraynoic acid (ETYA) considerably decreased N-OH-AAF activation while indomethacin or aspirin were not effective. Ram seminal vesicle microsomes activate N-OH-AAF apparently by prostaglandin synthetase. Our work indicates that N-OH-AAF was activated by lipoxygenase pathway in these cells. The 12L-hydroperoxy-5,8,10,14-icosatetraenoic acid (12-HPETE) generated through endogenous or exogenous arachidonate sources probably is the hydroperoxide substrate for the peroxidase. Platelets which are rich in lipoxygenase also activate N-OH-AAF. Since 12-HPETE is one of the three hydroperoxides found in animal kingdom, the peroxidase activation may have significant importance in mammary gland carcinogenesis. (no Refs)

32. THE EFFECT OF HOST AGE ON THE GROWTH OF TRANSPLANTABLE TUMORS IN MICE.

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N. N. Petrov Res. Inst. Oncology, USSR Ministry Health, Leningrad, USSR
Vopr Onkol; 27(8):52-59 1981

Tumors of various histological patterns (squamous-cell carcinoma of uterine cervix SCC, Lewis lung carcinoma, hepatoma-22a, mammary adenocarcinoma-755, sarcoma-180 and hemocytoblastosis La) were transplanted in mice aged 3, 12-18 mo. Tumor SCC, hepatoma-22a, sarcoma-180 and adenocarcinoma-755 grew faster in older animals (18 mo) than in younger ones (3 mo), while Lewis lung carcinoma and hemocytoblastosis La developed at the same rate in old and young animals. It is suggested that tumor growth in senescent organism is determined by both hormono-metabolic shifts, degree of immunologic vigor and a number of biological characteristics of tumor. (Author abstract) (26 Refs) (In RUS)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

33. MODULATION OF PROSTAGLANDINS IN HORMONE DEPENDENT MAMMARY CARCINOMA (MEETING ABSTRACT).

Foecking MK, Panganamala RV, Abou-Issa H, Minton JP
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International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Prostaglandin (PG) production may be hormonally modulated in hormone dependent mammary cancer. The purpose of this study was to relate the effects of in vivo hormone manipulations on tumor growth to accompanying changes in prostaglandin production. Mammary tumors were induced in female Sprague-Dawley rats by intubation of 5 mg of 7,12-dimethylbenz(a)anthracene (DMBA) at 4 weekly intervals. Prostaglandin production was measured as release of PG from tumor slices into an aqueous medium. PGs released into the medium increased with time up to one hr. The measurement of ng PG released/g tissue at 10 min was used for comparisons. Ovariectomy of tumor-bearing rats results in regression of the DMBA-induced mammary tumor 80-90% of the time. PGE2 production was increased 5-fold in regressing tumors compared to actively growing tumors. Non-regressing tumors from ovariectomized rats showed higher PGE2 production than growing tumors from intact rats, but not as high as the production in regressing tumors. 6-Ketoprostaglandin F1alpha release was measured to reflect prostacyclin production in the tumors. Production of 6-keto-PGF1alpha was elevated 2.5-fold in regressing tumors compared to growing tumors. The change in PG which is seen after hormone ablation suggests that PG production may be modulated by hormones such as estrogen, progesterone, and prol actin in the mammary tumors. (1 Ref)

34. ESTROGEN AND ANTIESTROGEN INDUCED PROTEINS IN HUMAN BREAST CANCER CELLS (MEETING ABSTRACT).

Iacobelli S, Sica G, Natoli C, Natoli V
Laboratorio Endocrinologia Molecolare, Universita Cattolica S. Cuore, 00168 Roma, Italy
Twelfth International Congress of Chemotherapy, July 19-24, 1981, Florence, Italy. The International Society of Chemotherapy 301 pp., 1981.

Estrogens are probably the most important steroids which stimulate the growth of human breast cancer. The only available specific marker of tumor response to estrogen is the progesterone receptor (PR). Since PR does not appear a perfect indicator for the response to estrogen and antiestrogen for tumor cell proliferation we have focused our attention on other estrogen-induced proteins that might be more closely related to tumor response to endocrine therapy. In 2 long-term human breast cancer cell lines and in 5 primary cultures derived from freshly obtained human breast cancer tissue estrogen was found to induce the synthesis of a secreted glyco-protein of mol wt 51,000 daltons. The 51k protein which accounts for 20-30% of 35S-methionine incorporation into secreted proteins was induced only in those cells containing high concentrations of estrogen receptors. The induction process was specific for steroids capable of interacting with the estrogen receptor. The antiestrogen tamoxifen, which prevented tumor cell growth stimulation by estrogen, inhibited the induction of the 51k protein by estradiol at a M ratio of 10,000. We propose that the 51k protein could represent an excellent marker for predicting hormone responsiveness of human breast cancer to estrogen and antiestrogen. (no Refs)

35. EVIDENCE FOR A NEW ROLE OF PITUITARY DERIVED HORMONES AND GROWTH FACTORS IN MAMMARY TUMOR CELL GROWTH IN VIVO AND IN VITRO (MEETING ABSTRACT).

Sirbasku DA, Officer JB, Leland FE, Iio M
Department of Biochemistry and Molecular Biology, The University of Texas Medical School, Houston, TX
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Evidence has been obtained that estrogen-responsive growth in vivo of the MTW9/PL rat mammary tumor cells can be stimulated 4.3-to 6.6-fold by coimplantation of the growth hormone (GH) and prolactin (PRL) secreting GH3/C14 rat pituitary tumor cells. The GH or PRL secreted by the GH3/C14 tumor could be directly mitogenic for MTW9/PL cells; neither of these hormones was seen to be mitogenic for MTW9/Pl cells over a broad range of concentration. We showed that elevated GH levels induced by the GH3/C14 tumor lead to 3-to 7-fold elevated levels of somatomedin C (SmC) in W/Fu rats. Thus, we asked whether SmC was mitogenic for MTW9/PL cells; up to 500 ng/ml SmC showed no mitogenic activity. Furthermore, MTW9/PL cells contain v ery low levels of SmC receptors. Elevated PRL could induce the production of as yet unrecognized factors which are then mitogenic for MTW9/PL cells. This is being directly tested now and preliminary data show that hypophysectomy causes a decrease in MTW9/PL growth factor activity in serum. The GH3/C14 tumors themselves in vivo produce growth factors which promote the growth of the MTW9/PL cells. Extracts of GH3/C14 tumors from estrogen-treated animals were prepared and assayed for mitogenic activity with MTW9/PL cells. These extracts showed a high specific growth factor activity which replaced the serum growth requirement of the MTW9/PL cells. Extracts of normal rat pituitary glands also showed growth factor activity toward MTW9/Pl cells, although the specific activity was 2.7 x less than that of the GH3/C14 tumors. (no Refs)

36. EFFECT OF ESTROGEN ON CELL PROLIFERATION, ULTRASTRUCTURE, AND SECRETORY PROTEINS IN HUMAN BREAST CANCER CELL LINES (MEETING ABSTRACT).

Rochefort H, Chalbos D, Coezy E, Vic P, Vignon F, Westley B, Garcia M
INSERUM U 148, 60 Rue de Navacelles, 34100 Montpellier, France
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

It is debated whether estrogens directly stimulate the growth of breast cancer. We have therefore looked to the effects of estrogens on two human breast cancer cell lines MCF7 and T47D established from pleural metastasis. The cells were cultured in medium containing 10 to 1% fetal calf serum (FSC) decreased in steroid after charcoal (DCC) treatment. Cell proliferation was evaluated by DNA assay (GABA) and protein synthesis by incorporation of 35S-methionine followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and fluorography. Estrogens at physiological concentrations: a) stimulated the growth of the two cell lines; b) altered the ultrastructure of the cells by increasing microvilli and blebs at the cell surface and by transforming 40% of them into secretory cells with secretory granules and Golgi saccules; c) stimulated the synthesis of glycoproteins which were released into the culture medium. One major protein was 46,000 daltons and 53,000 daltons mol wt for the MCF7 and the T47D respectively. Preliminary characterization of these proteins will be reported. The antiestrogens, tamoxifen and 4-hydroxytamoxifen, inhibited these three series of effect and displayed no stimulatory activity on these three parameters. Other steroid hormones were inactive as long as they did not activate the estrogen receptor. We conclude that estrogens are able to stimulate the growth of breast cancer cells in culture as previously reported by M Lippman. The mechanism of their effect either direct or permissive on factors present in the serum or indirect via the estrogen induced proteins secreted in the medium will be discussed. (no Refs)

37. STEROID METABOLISM AND OESTROGEN RECEPTORS IN HUMAN BREAST CARCINOMAS.

Miller WR, Hawkins RA, Forrest AP
Dept. Clinical Surgery, Univ. Edinburgh, Edinburgh, Scotland
Eur J Cancer Clin Oncol; 17(8):913-917 1981

Metabolism of 7alpha[3H] testosterone and estrogen receptor activity have been measured in 54 human breast cancers. All tumors converted testosterone to delta4 androstenedione, 5alpha dihydrotestosterone and 5alpha androstanediol, but unequivocal evidence for production of estradiol was obtained in only 29 of the tumors. Thirty-seven tumors were classified as estrogen receptor 'positive' containing levels in excess of 5 fmol/mg cytosol protein. Although mean conversions to delta4 androstenedione, 5alpha dihydrotestosterone and 5alpha androstanediol were all higher in estrogen receptor negative tumors as compared with receptor positive group, the differences did not reach statistical significance. There was, however, a significant trend for estradiol synthesis to be associated with estrogen receptor positive tumors (p less than 0.025). All tumors with very high level of receptors converted testosterone to estradiol. (Author abstract) (21 Refs)

38. CHARACTERIZATION OF A NEW HORMONALLY RESPONSIVE HUMAN BREAST CARCINOMA CELL LINE (MEETING ABSTRACT).

Wilson EL, Dutlow C, Dowdle EB
Department of Clinical Science and Immunology, Medical School, Observatory 7925, Cape Town, South Africa
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

A breast carcinoma cell line has been established from a bony metastasis taken from the femur of a 56 yr old woman. The cells grow in culture as an adherent monolayer which is organized in distinct acinar clusters. They have a doubling x of 60 hr in RPMI 1640 supplemented with 15% fetal bovine serum. No cell growth is observed if cells are cultured in medium to which steroid free fetal calf serum has been added and prolonged exposure to steroid free serum results in cell death. Cell viability can be preserved if steroid free serum is supplemented with insulin. The cells release large quantities (60 urokinase units/10(7) cells/24 hr) of a 70,000 mol wt plasminogen activator that is immunochemically distinct from urokinase. The plasminogen activator secreted by these cells can be inhibited by an antibody prepared against the enzyme secreted by melanoma cells cultured in vitro. These breast carcinoma cells also contain the mammary specific enzyme, lactose synthetase. Growth in vitro and 3H-thymidine incorporation into DNA were stimulated by insulin (0.1 ug/ml). Plasminogen activator synthesis was enhanced by insulin (0.1 ug/ml) and estrogen (10-10M) and inhibited by testosterone (10-10M). The availability of a new cell line with phenotypic markers and patterns of hormonal responsiveness characteristic of breast epithelium is of importance for the study of the cell biology of mammary neoplasia and our results emphasize the potential value of plasminogen activator synthesis as a measure of susceptibility to hormonal effects. (no Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

39. MONOCLONAL ANTIBODIES TO DIFFERENTIATION ANTIGENS OF NORMAL HUMAN MAMMARY EPITHELIAL CELLS (MEETING ABSTRACT).

Peterson JA, Moncada FR, Ceriani RL
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In Vitro; 17(3):225 1981

Hybridomas were prepared that secrete monoclonal antibodies to surface antigens of normal human mammary epithelial (HME) cells by fusion of mouse myeloma cells with spleen cells from BALB/c mice immunized with human milk fat globule (HMFG) membranes. Preliminary selection for presumptive breast specificity was based on specific binding to HMFG membranes and not to membranes from human mammary fibroblasts, or HeLa, HT-29, or lymphoblastic cell lines. Specificity of binding to HME cells was shown by competion with solubilized HMFG and with rabbit anti-HME antisera. Five different hybridomas have been prepared, all of which bind to surface antigens of normal HME cells while each binds differently to several human breast carcinoma cell lines, thus indicating a heterogeneity in surface antigens of breast tumors. We have previously shown that the HMFG membrane is made up of four major components, three of which contain antigens specific for HME cells. The monoclonal antibodies bind to at least two different mol wt components. These hybridomas will be useful in characterizing surface antigens of normal HME cells and in classifying breast tumors. (1 Ref)

40. DISTRIBUTION OF HLA CLASS 1 ANTIGENS IN NORMAL HUMAN TISSUES AND MAMMARY CANCER (MEETING ABSTRACT).

McGee JO, Fleming KA, McMichael J, Woods J, Morton J
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Br J Cancer; 43(4):564 1981

HLA antigens are glycoproteins which are presumed to be located exclusively on cell surfaces. These antigens are of two classes: Class 1 (HLA-A,B,C) and Class 2 (HLA-DR). It has been assumed from absorption experiments of HLA antisera with whole-tissue homogenates that these antigens are present in virtually all nucleated cells. HLA antigens modulate some cell-mediated immune responses by major histocompatibility complex (MHC) restriction of T-cell-mediated immunity. This is of proven relevance in immunity to viral infections, and may also be relevant to T-cell-mediated responses to tumor cells. In this paper, using monoclonal antibodies it is shown that HLA Class 2 antigens are expressed only on normal lymphoid cells, vascular endothelial, and certain types of epithelial cell (including mammary-duct epithelium). In contrast HLA (A,B,C) antigens are expressed in half of 19 human mammary cancers examined to date. A prospective study is underway to determine whether the expression of HLA Class 1 antigens on human mammary cancer cells is of prognostic significance since the natural history of these tumors is variable. (no Refs)

41. A VIRAL ANTIGEN AS A MARKER FOR THE PROGNOSIS OF HUMAN BREAST CANCER (MEETING ABSTRACT).

Keydar I, Selzer G, Chaitcik S, Hareuveni M, Karby S, Hizi A
Department of Microbiology, The George S. Wise Center for Life Sciences, Tel Aviv University, Ramat Aviv, Israel
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. 92 pp., 1981.

The presence of an antigen immunologically related to gp52 (a 52000 dalton glycoprotein of the mouse mammary tumor virus) in human breast cancer was reported a few yr ago. The possible use of this viral related antigen as a marker for the detection of human breast cancer was studied in an Israeli population. The results obtained show that the gp52 cross-reacting antigen is detected in 58.8% of Jews originating from Europe, whereas in Oriental Jews (African-Asian origin) the percentage of positive cases is much higher (74.5%) as tested by the immunoperoxidase assay. Furthermore, a retrospective study of 104 cases of breast cancer patients in stage 2, shows clearly that if the antigen is detected at the time of biopsy one can predict an unfavorable prognosis of the disease. (no Refs)

42. SERUM AND TISSUE CARCINOEMBRYONIC ANTIGEN IN BENIGN AND MALIGNANT LESIONS OF THE BREAST.

von Kleist S, Wittekind C, Polack M, Gropp H, Sandritter W
Forschergruppe Tumorimmunologie, Institut fur Immunobiologie der Universitat Freiburg, Stephan-Meier-Strasse 8, D-7800 Freiburg i. Br., W. Germany
Arch Geschwulstforsch; 51(6):523-526 1981

The serum (enzyme assay) and tissue (immunoperoxidase test) levels of carcinoembryonic antigen (CEA) were determined in 51 cases of breast cancer and in 33 benign breast lesions. CEA-positive tumors were found to be accompanied by low or negative CEA serum levels. The stage and histologic type of lesions were compared with the positivity and the increase of CEA. (5 Refs) (In FRE)

43. THE DISTRIBUTION OF COMMON ALL ANTIGEN (CALLA) IN NON-HEMATOPOIETIC TISSUES (MEETING ABSTRACT).

Metzgar RS, Borowitz M, Jones NH, Dowell BL
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

CALLA is defined by polyclonal and monoclonal xenogeneic antisera and is a 100,0 00 mol wt glycoprotein. We have recently tested the J-5 monoclonal antibody to CALLA on sections of various human adult and fetal tissues by immunoperoxidase staining. The following tissues demonstrated no significant immunohistochemical staining when compared to the P3 ascites control: fetal heart, liver, lung, pancreas, salivary gland, spleen and thymus, and adult skeletal muscle, spleen, tonsil and colon. Certain adult and fetal tissues, however, showed significant staining. In the adult kidney, most but not all the tubules stained intensely. Because of the large number of positive-staining tubules and their lower nuclear density compared to the nonstaining tubules, it appears that the

CALLA positive cells are in the proximal tubules. The pattern of staining in the tubules was apical, and sloughed or secreted antigenic material was present in the tubular lumens. In addition to the tubular staining, there was intense glomerular staining in fairly linear pattern along glomerular basement membranes. A similar staining pattern was present in fetal kidney. The fetal small intestine also showed apical staining of the epithelial cells of the villi, with some shedding of antigenic material noted. In contrast, a different pattern of staining was noted in adult breast. Although there was no significant staining of the breast epithelium, or the material within glandular lumens, there was staining around the myoepithelial cell layer of the breast. This was particularly prominent in the breast ducts but was also seen to some extent in the acini of the breast as well. (no Refs)

44. HUMAN MAMMARY EPITHELIAL ANTIGENS (HME-AGS) IN THE CIRCULATION OF NUDE MICE IMPLANTED WITH A BREAST TUMOR AND NON-BREAST TUMORS.

Sasaki M, Peterson JA, Wara WM, Ceriani RL
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Cancer; 48(10):2204-2210 1981

Human mammary epithelial antigens (HME-Ags) obtained from the membrane of the human milk fat globule (HMFG) were tested for their possible role as breast tumor markers. Specific antisera raised against HME-Ags were used to monitor plasma concentrations of these antigens in nude mice implanted with a human breast tumor. The level of plasma HME-Ags, determined by radioimmunoassay, was significantly higher in animals transplanted with a human breast tumor (mean +- standard error; 687 +-184 ng/ml) than those with other types of human tumors (colon carcinoma: 50 +-29; lung carcinoma: 82 +-78; medulloblastoma: less than 30; and Wilson melanoma: less than 30) and healthy control animals (49 +-22). Removal of the breast tumor resulted in a significant drop of HME-Ags level to 'background' values, suggesting that animals with the breast tumor did release into the circulation HME-Ags which could be possibly used as breast-tumor markers in breast tumor diagnosis. (Author abstract) (24 Refs)

45. URINARY CANCER-RELATED PROTEIN, EDC1, AS IMMUNODIAGNOSTIC MARKER IN BREAST CANCER (MEETING ABSTRACT).

Chawla RK, Miller FW, Lawson DH, Richmond A, Rudman D
Department of Medicine, Emory University, Atlanta, GA
Second Annual NCI/EPA/NIOSH Collaborative Workshop: Progress on Joint Environmental and Occupational Cancer Studies, September 9-11, 1981, Rockville, Maryland. National Cancer Institute 33 pp., 1981.

A novel glycoprotein labeled EDC1, mol wt 27.5 K, was isolated originally from the urine of a leukemic patient ED. This protein inhibited trypsin, chymotrypsin and human plasmin and was immunologically related to a normal plasma protein inter-alpha trypsin inhibitor (IATI) mol wt 160 K. By using a specific and sensitive radioimmunoassay for EDC1, urinary levels of this protein were measured in i) normal healthy women, ii) women with metastatic breast cancer, iii) patients with non-neoplastic diseases, and iv) preoperative patients with localized breast mass. The urinary excretion of EDC1 (mg/g creatinine) was classified in four ranges; i) normal less than 15 mg; ii) light 15-30 mg; iii) intermediate 31-45 mg; and iv) heavy greater than 45 mg. The av +/- SEM values were as follows: 8.0+/-2.2 for normal women and 98.6+/-11 for metastatic breast cancer patients. In the 26 preoperative patients, subsequently shown to have benign lesions, the EDC1 excretion was 21.5+/-3.4; 24 of these patients were in the normal to light and 2 were in the intermediate range of excretion. In the other preoperative subgroup (27 patients subsequently shown to have malignant lesions), the av EDC1 excretion was 43.1+/-7.6 mg with 8 normal, 5 light, 4 intermediate and 10 heavy excretors. A direct correlation existed between the number of nodes and the level of EDC1. Further analysis showed a negative correlation between plasma levels of IATI and urinary EDC1 levels in metastatic breast cancer patients. In normal plasma, the immunoreactive (IR)-IATI material was found to exist in three molecular forms viz with mol wt 160 K, 110 K and 60 K. In patients with metastatic breast cancer, who were heavy excretors of EDC1, the IR-IATI corresponding to mol wt 60 K was absent and their total IR-IATI was about 2/3 of that in normals. When normal plasma was incubated with trypsin or with human plasmin for 4 hr, the IR-IATI shifted to the mol wt 30 K region. These data suggest that in cancer urinary EDC1 may arise as a result of selective degradation of IATI by cancer-associated proteolysis and that IATI may be one of the primary inhibitors for this enzymatic activity. (no Refs)

46. TOPOGRAPHICAL ANALYSIS OF VIRAL EPITOPES USING MONOCLONAL ANTIBODIES: MECHANISM OF VIRUS NEUTRALIZATION.

Massey RJ, Schochetman G
Biological Carcinogenesis Program, Frederick Cancer Res. Center, Frederick, MD, 21701
Virology; 115(1):20-32 1981

The mouse mammary tumor virus (MMTV) was used in neutralization studies with monoclonal antibodies (monoclones) to the major external glycoprotein gp52. Monoclones to MMTV gp52 showed that epitopes with different antigenic specificities were targets for virus neutralization. These epitopes were group specific (common to C3H, GR, RIII, and C3Hf MMTVs), class specific (common to C3H and GR MMTVs), and type specific (unique to C3H MMTV). Competitive antibody binding assays using a radioiodinated C3H MMTV type-specific neutralizing monoclone revealed that all the monoclones that neutralized virus infectivity also blocked the binding of the type-specific monoclone to C3H MMTV. A topographically distinct site from this determinant was found using other monoclones which did not compete for the binding of the type-specific monoclone and their epitopes did not function as targets for neutralizing antibodies. However, these non-neutralizing monoclones could neutralize virus infectivity in the presence of antimouse IgG sera. Therefore, two topographically distinct sites could be identified on a single protein of the virus. One site functioned as a target for neutralization and the second site bound antibody but did not affect neutralization. The observation that virus bound to cells was no longer susceptible to neutralization by monoclones showed that neutralization affected virus prior to its binding to cell surface receptors. This result further indicated that antibody prevented virus adsorption to cells and that neutralization was mediated by steric hindrance from antibodies binding to epitopes adjacent to those determinants which functioned in virus binding to cell surface receptors. (Author abstract) (33 Refs)

47. EVIDENCE FOR THE ASSOCIATION OF TWO CELL SURFACE GLYCOPROTEINS OF 13762 MAMMARY ASCITES TUMOR CELLS: CONCANAVALIN A-INDUCED REDISTRIBUTION OF PEANUT AGGLUTININ-BINDING PROTEINS.

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Dept. Biochemistry, Oklahoma State Univ., Stillwater, OK, 74078
Exp Cell Res; 135(2):418-424 1981

The behavior of the cell surface concanavalin A (con A) receptors and of peanut agglutinin (PNA) receptors on the MAT-B1 ascites subline of the 13762 rat mammary adenocarcinoma was examined using fluorescein-labeled conA and PNA. ASGP-1, the major glucosamine-containing glycoprotein of these ascites cells, is the only PNA-binding protein observed by dodecyl sulfate electrophoresis. ASGP-2, the second most prominent component after glucosamine labeling, is the most abundant conA-binding protein. These two glycoproteins were previously shown to be associated as a complex in detergent extracts of the cells. ConA-binding proteins, upon incubation with fluorescein-labeled conA (FITC-conA), redistribute on the cell surface into small and large aggregates similar, but not identical, to those seen in 'patching' and 'ca pping' experiments with lymphocytes. PNA-binding proteins failed to redistribute during incubation with fluorescein-labeled PNA (FITC-PNA) and appeared in a diffusely stained pattern around the circumference of the cells. However, when cells were treated with unlabeled conA followed by FITC-PNA, or with FITC-PNA followed by unlabeled conA, there was marked redistribution of the FITC-PNA. These results indicate that ASGP-1 redistributes in response to the movement of conA-binding proteins and supports our hypothesis that ASGP-1 and ASGP-2 are associated on the plasma membrane at the cell surface as well as in detergent extracts. (Author abstract) (22 Refs)

48. EFFECT OF THE AGE-RELATED IMMUNE DEPRESSION INDUCED BY MTV ON THE IN VIVO GROWTH OF A MAMMARY CARCINOMA.

Tagliabue A, Luini W, De Vito G, Boraschi D
Istituti di Ricerche Farmacologiche 'Mario Negri', Via Eritrea 62, 20157 Milan, Italy
Br J Cancer; 44(3):460-463 1981

The interactions between immune responses and mouse mammary tumor virus (MTV) were studied in C3H/HeN mice. MTV-infected and MTV-free mice were immunized with sheep RBC and the splenocytes were tested for their ability to produce antibodies against MTV. Significant depression of plaque-forming cells was observed in 14-20 wk old MTV-infected mice, compared with MTV-free mice of the same age. The immune response of 8 and 36 wk old MTV-infected mice was almost similar to that of age-matched MTV-free mice. Analysis of the in vivo growth of transplanted mammary gland carcinoma showed that median survival times and median latent periods in MTV-infected mice were shorter than those in MTV-free mice. (18 Refs)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

49. POSSIBLE ROLE OF GENETIC CELL VARIANTS IN THE VIRAL INDUCTION OF MOUSE MAMMARY TUMORS.

Lasfargues EY, Lasfargues JC
Inst. Medical Res., Copewood St., Camden, NJ, 08103
In Vitro; 17(9):805-810 1981

Out of three attempts to induce neoplasia in normal C57Bl mammary epithelial cells with the mouse mammary tumor virus (MuMTV) only one presented signs of tumorigenicity. Immunofluorescence showed that virus synthesis took place in all three sublines but tumorigenicity as detected by cell aggregation viability (CAV) and transplantation into syngeneic mice failed to occur in two of them. By comparison, cells from a BALB/c spontaneous mammary tumor that do not express MuMTV were 100% tumorigenic, whereas cells from a BALB/cfC3H tumor with a 95% virus-producing cell population had a normal CAV and were tumorigenic only in 60% of the test animals. This lack of correlation suggested that many of the virus-producing cells were not neoplastic and that neoplasia might occur under virus stimulation only if a restricted population of genetic cell variants existed. Accelerated tissue culture passages of virus-free C57Bl and BA LB/c normal mammary cells resulted in their spontaneous neoplasia at Passages 23 and 50, respectively; when duplicated cells cryopreserved in early passages were revived and cultivated in the same manner, neoplasia occurred at Passages 27 and 58. The similarity of the passage numbers appears to confirm the existence of genetic cell variants among the normal cell population. (Author abstract) (16 Refs)

50. CHEMICAL-VIRAL CO-CARCINOGENESIS IN VITRO USING CLONED MAMMARY EPITHELIAL CELLS AND MOUSE MAMMARY TUMOR VIRUS (MEETING ABSTRACT).

Howard DK, Fisher PB, Schlom J
National Cancer Institute, National Institutes of Health, Bethesda, MD, 20205
In Vitro; 17(3):236 1981

We have evaluated the effect of mouse mammary tumor virus (MMTV) and 7,12-dimethylbenz(a)anthracene (DMBA), either alone or in combination, on mammary epithelial cells in vitro. A single-cell clone (clone 2), was derived from the normal mouse mammary gland cell line, C57MG, and was shown to be of murine origin by karyotyping, isoenzyme analyses, and by immunofluorescence using species-specific antisera. This clone failed to induce tumors in syngeneic or athymic (nude) mice. The epithelial origin of the cells was demonstrated by the presence of desmosomes, tonofibrils and secretory granules. Clone 2 cells were infected with MMTV host-range variant MMTV (RIII) vp4, and both infected and mock-infected cultures were treated with DMBA. Cultures treated with both virus and carcinogen exhibited morphological changes and a slight increase in ability to grow in soft agar after 5 to 7 subcultures. The most striking alteration in the phenotype of cells exposed to the combination of MMTV and DMBA, however, was an increase in their tumorigenic potential in athymic mice. Cultures treated with virus alone or DMBA alone did not show an increase in tumorigenicity. This cell-culture model system now permits the study of the interaction of chemicals and MMTV in the initiation and promotion of mammary cell transformation. (no Refs)

51. GLUCOCORTICOIDS REGULATE EXPRESSION OF DIHYDROFOLATE REDUCTASE CDNA IN MOUSE MAMMARY TUMOUR VIRUS CHIMAERIC PLASMIDS.

Lee F, Mulligan R, Berg P, Ringold G
Dept. Pharmacology, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Nature; 294(5838):228-232 1981

Fusions between the mouse mammary tumor virus long terminal repeat and a mouse dihydrofolate reductase cDNA have been constructed in a SV40 vector. When these plasmids are transferred into recipient cells, the production of dihydrofolate reductase is regulated by glucocorticoid hormones. These results define a hormonally responsive region of the viral genome. (Author abstract) (26 Refs)

52. EXPRESSION OF THE MURINE MAMMARY TUMOR VIRUS IN THE MILK OF F1 HYBRIDS OF VIRUS NEGATIVE MOUSE STRAINS.

Bentvelzen P
Radiobiological Inst. TNO, Rijswijk, The Netherlands
Eur J Cancer Clin Oncol; 17(8):883-888 1981

Milk samples of multiparous females from several mouse strains and their F1 hybrids were tested for the presence of the envelope glycoprotein gp52 of the murine mammary tumor virus. F1 hybrids resulting from matings of the virus negative strain BALB/c with the virus negative strains AKR, ND2 or RFM were positive for the viral antigen. The progeny of backcrosses to either parent had considerable lower incidences of viral antigen-positive milks. It was concluded that different recessive genes in the BALB/c strain on the one hand and in the AKR, ND2 and RFM strain on the other cause inhibition of endogenous virus expression. In F1 hybrids the two sets of genes complement each other, resulting in virus release. (Author abstract) (31 Refs)

53. INDUCTION OF ENDOGENOUS MAMMARY TUMOR VIRUS EXPRESSION DURING HORMONAL INDUCTION OF MAMMARY ADENOACANTHOMAS AND CARCINOMAS OF BALB/C FEMALE MICE.

McGrath CM, Prass WA, Maloney TM, Jones RF
Dept. Tumor Biology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
JNCI; 67(4):841-852 1981

Treatment of BALB/c female mice with pituitary isografts, under conditions that established mammary hyperplasia in an anovulatory condition, enhanced mammary tumor development with prior onset of dysplastic foci in lobular parenchyma. Tumor onset began at 8 mo (mean onset time, 18 mo); the 25-mo incidence was 100%. Adenoacanthomatous tumors appeared first. Adenocarcinomas appeared only after more than 14 mo of continuous hormone stimulation. Dysplastic and neoplastic changes occurred while blood levels of the three major mammotropic hormones were physiologic. Murine mammary tumor virus (MuMTV) p28 was detected in all tumors tested, independent of time of tumor appearance or tumor type, although keratinizing cells in adenoacanthomatous tumors did not contribute to MuMTV antigen expression. MuMTV gp52 was detected in only a small fraction of cells in a few tumors. MuMTV RNA contents were above normal in all tumors tested. Neither MuMTV structural antigens nor RNA was induced in normal glands by the same hormone treatment that ultimately resulted in dysplasia and tumor formation and elevated levels of these viral markers in neoplasms. The MuMTV RNA in all hormone-induced tumors was readily distinguishable in base sequence from standard MuMTV RNA but indistinguishable from MuMTV RNA recovered from lactating mammary glands of BALB/c females carrying only endogenous MuMTV proviruses, suggesting that endogenous MuMTV RNA sequences were induced in hormone-induced neoplasms. RNA indistinguishable from MuMTV sequences present in hormone-induced primary tumors was also detected in multiple genomic equivalents in two independently derived hormone-induced premalignant alveolar hyperplasias. MuMTV p28 was detected, but gp52 was not. The same hormone stimulu s that generated 100% tumors in normal glands greatly accelerated tumor development in premalignant hyperplasias but did not amplify MuMTV RNA or antigens in either hyperplasias or the tumors derived from them. B-type virions were not detected in these tissues, in either hypophyseal implant-stimulated or virgin hosts. Cell-free virions were not detected in culture. These data suggest that the replication of MuMTV induced in hormone-induced neoplasms is defective. Details of its expression suggest that if involved in events leading to tumors, its involvement is insufficient cause for those tumors. (Author abstract) (41 Refs)

54. CLONED MOUSE MAMMARY TUMOR VIRUS DNA IS BIOLOGICALLY ACTIVE IN TRANSFECTED MOUSE CELLS AND ITS EXPRESSION IS STIMULATED GLUCOCORTICOID HORMONES (MEETING ABSTRACT).

Buetti E, Diggelmann H
Institut Suisse de Recherches Experimentales sur le Cancer, CH-1066 Epalinges, Switzerland
Experientia; 37(6):640 1981

We have cloned circular unintegrated mouse mammary tumor virus (MMTV) DNA from infected rat hepatoma cells in bacteriophage lambda. Seven independent clones containing MMTV DNA of homogeneous length of 9 kilobase (kb) (5) or 10 kb (2) were identified. The 5 9-kb clones had identical restriction maps consistent with that of 9 kb unintegrated DNA, the other 2 were aberrant. MMTV DNA inserts were purified, ligated and used for cotransfection of Ltk- cells together with a plasmid containing the thymidine kinase gene of herpes simplex virus. All Tk+ cell clones acquired new MMTV sequences and those transfected with the 9 kb MMTV DNA synthesized normal viral RNA and proteins. Viral gene expression was increased by the addition of dexamethasome. (no Refs)

55. THE ENDOGENOUS PROVIRAL MOUSE MAMMARY TUMOR VIRUS GENES OF THE GR MOUSE ARE NOT IDENTICAL AND ONLY ONE CORRESPONDS TO THE EXOGENOUS VIRUS.

Herrlich P, Hynes NE, Ponta H, Rahmsdorf U, Kennedy N, Groner B
Institut fur Genetik und fur Toxikologie, Kernforschungszentrum Karlsruhe, Postfach 3640, D 7500 Karlsruhe 1, W. Germany
Nucleic Acids Res; 9(19):4981-4995 1981

The endogenous proviral copies of mouse mammary tumor virus (MMTV) were selected from a gene library of GR mouse DNA. We obtained five different lambdaMMTV recombinant clones. Four of them correspond to the 3' Eco RI fragments of the endogenous proviruses and one comprises an intact MMTV provirus with 2 to 3 kb of flanking mouse genomic DNA. Heteroduplex formation followed by S1 digestion under stringent conditions shows that there is nucleotide sequence heterology among the cloned endogenous proviral copies. Only one endogenous proviral copy, associated with the mtv-2 locus, was found to be totally homologous to the exogenous proviral DNA. (Author abstract) (22 Refs)

56. DNA SEQUENCE ANALYSIS OF THE LARGE TERMINAL REPEAT OF MOUSE MAMMARY TUMOR VIRUS (MMTV) DNA (MEETING ABSTRACT).

Fasel N, Pearson KW, Buetti E
Institut Suisse de Recherches Experimentales sur le Cancer, CH-1066 Epalinges, Switzerland
Experientia; 37(6):644 1981

Large terminal repeats (LTR) of MMTV DNA might play an important role in the integration of viral DNA into the host genome. The restriction enzyme fragment containing the LTR might also harbor the sequences necessary for the glucocorticoid sensitivity of viral gene expression. Therefore we decided to sequence this 1.5-kb fragment derived from circular MMTV DNA clones in phage. For this purpose, we subcloned all of the Pst I fragments in the plasmid pBR 322 prior to sequence analysis. (no Refs)

57. COVERT INFECTION OF A MOUSE MAMMARY TUMOR CELL LINE WITH M. HYORHINIS: COSEDIMENTATION WITH MMTV (MEETING ABSTRACT).

Sydiskis RJ, Weber PA, DelGiudice RA
Department of Microbiology, University of Maryland, Dental School, Baltimore, MD, 21201
In Vitro; 17(3):207 1981

Supernatants from cultures of a mouse mammary tumor (MT) cell line were found to produce a specific cell detachment effect when inoculated into HeLa cells. The repeated attempts to cultivate this cell detachment factor (CDF) in bacteriologic, fungal, and mycoplasma media were unsuccessful. However, using the DNA fluorochrome staining technique and specific immunofluorescent staining procedures, the CDF was positively identified as a 'noncultivable' strain of Mycoplasma hyorhinis. It was also noted that this CDF could be labeled with 3H-uridine in MT cell cultures, concentrated and banded at a density of 1.18 g/cm3 when centrifuged to equilibrium in a 20-60% sucrose gradient. The salient feature of these studies is that M hyorhinis sediments at the exact density of mouse mammary tumor virus (MMTV) in sucrose gradients. This was demonstrated by sucrose gradient analyses of a purified sample of MMTV, assaying for reverse transcriptase activity, and a 3H-uridine labeled sample of M hyorhinis. The covert presence of M hyorhinis should be of particular interest and concern to researchers working with MMTV. The presence of this 'noncultivable' strain of mycoplasma in MMTV-producing cell lines could go undetected and result in the simultaneous concentration of both MMTV and M hyorhinis during routine concentration and purification procedures for MMTV. (no Refs)

58. RADIATION EQUIVALENCY OF ENVIRONMENTAL CARCINOGENS: ASSAY SPECIFICITY (MEETING ABSTRACT).

Stevens RH, Cole DA
Department of Radiology, University of Iowa, Iowa City, IA, 52242
Clin Chem; 27(6):1066 1981

A major health concern for any new drug or chemical introduced in our population is its potential for inducing cancer. The presently utilized National Cancer Institute bioassay for carcinogenicity requires between two to four yr of continuous animal maintenance prior to tissue analysis and costs ranging anywhere from 300,000-500,000 dollars per substance. We have recently developed an in vivo assay designed to overcome these deficiencies based upon the induction of antitumor cell-mediated immunity (CMI) upon exposure to carcinogens compared with the levels brought about by exposure of only the hypoxic ileum and jejunum to x-rays. This allows mutagenicity/carcinogenicity to be expressed in terms of moles/rad. The procedure involves determining the increased injury to cultured x-ray induced small bowel adenocarcinoma cells as reflected in increased release of their radioiodinated membrane proteins brought about by peripheral blood lymphoid cells (PBLC) obtained from exposed rats. The present study was undertaken to establish the specificity for such measurements. The findings indicate that cytotoxic PBLC to the intestinal cancer tissues that were induced by x-rays and chemicals were not induced by nonspecific forms of injury (radiation or surgery), substances inducing cancer in other than gastrointestinal tissues (asbestos induced mesothelioma) or spontaneously arising tumors (breast or prostate). Conclusions from the study are that immunological measurements can be utilized to readily determine the mutagenicity/carcinogenicity potential of a drug. (1 Ref)

RADIOLOGICAL ASPECTS OF MAMMARY GLAND CARCINOGENESIS

59. RADIATION CARCINOGENESIS. COMPREHENSIVE FINAL REPORT, 16 MAY 1979-31 DECEMBER 1980.

Warren S, Brown CE, Gates O

Cancer Res. Inst., New England Deaconess Hosp., Boston, MA

Radiation Carcinogenesis. Comprehensive Final Report, 16 May 1979-31 December 1980. Available from National Technical Information Service, Springfield, VA, as DOE/EV/03017-43:, 29 pp., 1981.

This abstract covers three main areas of investigation: mesothelioma induction by asbestos, radiation tumorigenesis and transplantable tumors. Canadian and Rhodesian asbestos fibers have been administered under anesthesia to rats by intratracheal, intrapleural and ip injection. Additional groups were given 3-methylcholanthrene or x-radiation along with asbestos. A large series of mice also treated as above have displayed mesotheliomas. In addition, glass fiber injections and feeding of asbestos were done and have produced negative results to date. The carcinogenic effect of whole-body radiation on hemi-irradiated parabiont partners exposed to a single 1,000 R dose of x-ray was evidenced by a significant increase in the incidence of malignant tumors in only six tissues: skin, supporting soft tissue, kidney, bone, pancreatic islets and ovary. In the male adrenal medulla and in the female breast genetic and parabiotic hormonal factors were judged to exert a significant effect. The occurrence of incisional (anastomotic) sarcomas in significant numbers in hemi-irradiated and parabiont control pairs suggests the operation of mechanical factors complicating the healing process, only slightly enhanced by radiation. One of the very valuable but unanticipated developments of the rat radiation program was the isolation of two transplantable endocrine tumors with strong hormonal potentials: an insulinoma of the pancreas and a pheochromocytoma of the adrenal medulla. (Author abstract)

60. THE EFFECT OF INTERVAL BETWEEN NEUTRON RADIATION AND DIETHYLSTILBESTROL ON MAMMARY CARCINOGENESIS IN FEMALE ACI RATS (MEETING ABSTRACT).

Shellabarger CJ, Stone JP, Holtzman S
Brookhaven National Laboratory, Upton, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Both radiation and diethylstilbestrol (DES) are carcinogens for the mammary gland of ACI female rats. When DES is given at about the same time as radiation, DES and radiation interact in a synergistic fashion particularly in regard to the number of mammary adenocarcinomas per rat. We have studied the effect of increasing the time interval between radiation and DES on the capacity of DES to enhance (promote?) radiation-induced mammary carcinogenesis. DES, in the form of a compressed pellet containing a mixture of cholesterol and DES, formulated to av 1.25 mg of DES per 100 g of body wt, was given to groups of approx 28 rats at either 2 days before, or 50, or 100, or 200 days after 0.064 Gray of 0.43 meV neutron radiation. At each time that DES was given to irradiated rats, DES was also given to non-irradiated rats. All rats were studied for 375 days after the date of the DES administration. When the total number of mammary adenocarcinomas was calculated as a percentage of 24 sites per rat at-risk, DES and radiation always produced a response that was larger than the sum of the responses of DES alone plus radiation alone. This result suggests that these two agents can interact in a synergistic fashion. The interaction between radiation and DES did not decline as the time interval between radiation and DES was lengthened. This result suggests that radiation-induced (initiated?) mammary carcinogenesis is not subject to repair since DES enhancement (promotion?) continues to be effective over long time intervals. (no Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

61. ABNORMAL NIPPLE ASPIRATE CYTOLOGY AND PROLIFERATIVE CHANGES ASSOCIATED WITH MALIGNANT BREAST DISEASE (MEETING ABSTRACT).

King EB, Chew K, Ernster VL, Barrett DL, Petrakis NL
Department of Epidemiology and International Health, University of California, San Francisco, CA
Twenty-ninth Annual Scientific Meeting of the American Society of Cytology, November 2-7, 1981, St. Louis, Missouri. 90 pp., 1981.

Satisfactory nipple aspirate cytology samples were obtained from 34 of 82 malignant breasts prior to surgery and evaluated for cellularity, the distribution of epithelial cells, and cellular abnormalities. Tissue from each breast was reviewed independently and the histologic type of malignancy identified; the presence of benign lesions, including atypical epithelial proliferative disease (APD) was noted. Comparisons were made between these 34 malignant breasts, 61 breasts diagnosed as benign without APD, and 39 breasts diagnosed as benign with APD. We found that women with abnormal cytology (moderate and marked atypical hyperplasia) have a 6.4 x greater risk of breast cancer than women with no cytologic abnormalities. Comparisons between the two benign groups showed that women with atypical cytology had a 3.6 x greater risk of APD than women with normal cytology. APD was present in 27 malignant cases (80%) and in 39 benign cases (39%). We also found that women with the cytologic findings of epithelial cells in papillary groupings had 4.0 x greater risk of having breast cancer than women who had no papillary groupings on cytology. Our findings show cytopathologic changes in duct secretions to be associated with APD and breast cancer. If APD is an intermediate step in the malignant transformation of duct epithelium, the cytology of nipple secretions may have a role in the identification of women at risk for breast cancer. (no Refs)

62. PREFERENTIAL ACCUMULATION OF IRON IN HYPERPLASTIC TISSUE OF RAT MAMMARY GLAND.

Vijayaraghavan S, Rivera EM
Dept. Zoology, Michigan State Univ., East Lansing, MI, 48824
Proc Soc Exp Biol Med; 168(2):151-154 1981

The preferential accumulation of iron in rat hyperplastic alveolar nodules over tumors or normal mammary tissue is investigated. Hyperplastic nodule outgrowths and mammary tumors originally induced by 7,12 dimethylbenz(a)anthracene (DMBA: 20 mg), along with normal mammary tissue were analyzed for iron by the o-phenanthroline method. Total protein content was also determined in some cases. Results showed mean iron values for hyperplasias, tumors, and normal mammary tissue to be 176, 38, and 43 ug/100 mg dry wt, respectively. Iron values expressed per mg protein show hyperplasias with 4 to 13x more iron than normal and tumors with 3 to 16x more iron than normal tissue. Preferential accumulations of iron in DMBA-induced and spontaneous hyperplasias of rat mammary gland with elevated iron levels compared to that of liver and spleen was clearly indicated. This is in striking contrast to the resistance of rat liver hyperplastic nodules to accumulate iron. Although the significance of iron accumulation in mammary hyperplasias is unknown, there is increasing evidence that alterations in iron metabolism and ferritin are associated with breast and other cancers. Further investigation of the sequestering of iron in mammary hyperplasia related to their growth and oncogenic potential are needed. (25 Refs)

63. ESTROGEN AND PROGESTERONE RECEPTORS IN HUMAN BREAST CANCER: FREQUENCY AND DISTRIBUTION (MEETING ABSTRACT).

Zachariah NY, Chakmakjian ZH
Section of Endocrinology and Metabolism, Baylor University Medical Center, Dallas, TX, 75246
Clin Chem; 27(6):1077 1981

Determination of estrogen receptor (ER) and progesterone receptor (PR) has been useful in selecting patients for endocrine therapy. Using the conventional methods of determination, we have analyzed over 500 breast tumors for ER and PR; and classified them as positive (greater than 10fm/mg) negative (less than 3fm/mg) and borderline positive (4-9fm/mg). Fifty-two % of tumors were ER positive. However, 36% of the tumors were positive for both ER and PR. In order to establish the relationship between ER and PR in individual tumors, the quantitative correlation was studied in ER and PR positive tumors. It was found that 66.6% of the tumors were PR positive when ER was in the range of 10-40fm/mg; 78.2% PR positive when ER was 41-60fm/mg; and 85% PR positive when ER was 81-100fm/mg. Influence of menopausal status on the distribution of receptors indicate that 53.4% of post-menopausal women were ER positive while only 34.8% pre-menopausal women were ER positive. The ER content was also found to be higher in post-menopausal women. (ER in postmenopausal 55.8fm/mg, while in pre-menopausal 29.3fm/mg). Menopausal status did not have a significant influence on PR distribution or the content. Also, quantitative relationship between ER and PR with respect to menopausal status indicates that a strong correlation exists in pre-menopausal patients. Similar correlation was not possible in post-menopausal patients. This study shows that: (a) definite influence of menopausal status on ER; its distribution and content (b) greater the ER content, more the chance for tumor to be PR positive (c) frequency of ER and PR positive tumors correlate with the reported clinical response. (no Refs)

64. DISTRIBUTION OF CYTOPLASMIC AND NUCLEAR ESTROGEN RECEPTORS IN HUMAN BREAST CANCER (MEETING ABSTRACT).

Genz T, Eiletz J
Universitats-Frauenklinik Charlottenburg, Berlin, W. Germany
Acta Endocrinol [Suppl]; 96(240):123 1981

In our study estrogen receptor levels were measured in both compartments of breast cancer tissues. Cytoplasmic estrogen and progesterone receptors were determined by the dextran-coated charcoal technique. Measurement of nuclear binding sites was performed by an exchange assay with some modifications according to Bayard et al. For any sample to be classed as positive in terms of estrogen receptors it had to satisfy the following criteria: yield an unambiguous Scatchard line, levels of 20 fmol/mg pr otein and 25 fmol/mg DNA for cytoplasmic and nuclear binding sites, respectively. Nuclear receptor values ranged from 25-3,000 fmol/mg DNA with a dissociation constant of approx 3 x 10(-9) M to 12 x 10(-10) M. Eighty tissues (59%) with positive cytoplasmic estrogen receptor contained significant levels of nuclear binding sites in 84.3% of the specimens with and in 73.9% of the specimens without additional cytoplasmic progesterone receptors. Estrogen receptor negative tumors had low levels of nuclear binding sites in 17% only. Different results in receptor distribution in both fractions were found in approx 20% of all breast cancer cells. Preliminary clinical results indicate that the additional measurement of nuclear binding sites for estradiol may give more detailed information about hormone dependence. Fourteen women with metastatic disease could be analyzed. Nine of them had an objective remission undergoing hormone therapy. There was a good correlation between positive as well as negative cytoplasmic and nuclear binding sites in responders and non-responders, respectively. (no Refs)

65. GLUCOSE-6-PHOSPHATE DEHYDROGENASE ACTIVITY IN HUMAN BREAST CANCER: LACK OF ASSOCIATION WITH OESTROGEN RECEPTOR CONTENT.

Poulsen HS, Frederiksen P
Inst. Cancer Res., Radiumstationen, Aarhus Kommunehospital, DK-8000 Aarhus C, Denmark
Acta Pathol Microbiol Scand [A]; 89(4):263-270 1981

The correlation between glucose-6-phosphate dehydrogenase activity and different tumor characteristics was investigated in human breast cancer tissue. The enzyme activity was measured by a histochemical method and the estrogen receptor content by a dextran-coated charcoal assay. The proliferative activity of the tumors correlated positively with the glucose-6-phosphate dehydrogenase activity. No correlation was found between enzyme activity and tumor type and menopausal status, age, TNM-class nor estrogen receptor content. Based on this investigation it is concluded that the activity of glucose-6-phosphate dehydrogenase reflects the proliferative status of the tumor but not the hormone dependency of the tumor. (Author abstract) (24 Refs)

66. HISTOCHEMICAL DETERMINATION OF SEX-STEROID RECEPTORS IN HUMAN BREAST TUMORS. COMPARISON TO HISTOPATHOLOGY AND DCC-METHOD (MEETING ABSTRACT).

Czerwenka K, Bohm M, Binder B
Department of Pathology, University of Vienna, Vienna, Austria
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. 92 pp., 1981.

In the cases of human breast tumors tested so far, the presence of estrogen and progesterone receptors was determined by histo- and biochemical methods. For the histochemical method, the following steroid derivatives were used on frozen sections: 17 beta-estradiol hemisuccinate, 17 beta-estradiol-6-carboxymethyloxime, 11-hydroxyprogesterone hemisuccinate attached to bovine serum albumin as a carri er protein and labeled with fluoroscein isothiocyanate or TMRITC as fluorochrome. By an excess of the corresponding hormones the staining could be blocked. For the biochemical method, the dextran-coated charcoal assay (DCC) was applied. Furthermore, we correlated the quantity of the estrogen and progesterone receptors with different histomorphological parameters (type, tumor grade, epithelial cellularity, lymphocytic infiltration, lymph node metastases). The correlation between bio- and histochemical method was 86% for estrogen, and 74% for progesterone receptor. Generally, the differences are gradual, because the histochemical method is only semiquantitative, and the tumor itself usually greatly heterogeneous. Histologically, the majority of the tumors consisted of invasive ductal carcinomas not otherwise specified (IDC-NOS); cytomorphologically, the tumor grades were in the middle group (II). (no Refs)

67. ISOELECTRIC FOCUSING OF OESTRADIOL RECEPTOR PROTEIN FROM HUMAN MAMMARY CARCINOMA A COMPARISON WITH THE DEXTRAN-COATED CHARCOAL ASSAY (MEETING ABSTRACT).

Lloyd EJ, Barnes DM, Skinner LG
Christie Hospital, Manchester M20 9BX, England
Br J Cancer; 43(5):717 1981

A laboratory method for the detection of estradiol-17beta receptor protein (REc) in breast tumor tissue by isoelectric focusing (IEF) in polyacrylamide gel was investigaged. The results obtained by this method were compared to those from the dextran-coated charcoal method (DCC). A modified IEF method was used to investigate 32 cytosols prepared from unselected breast-tumor tissue. The results, when compared with DCC results obtained on the same cytosol, agreed on the presence or absence or receptors in 97% of cases. Quantitative analysis of the positive results showed a correlation coefficient of 0.88. However, IEF gave significantly lower receptor concentrations than the DCC method. Twenty-six Tru-cut biopsy tumor specimens were pre-incubated with radioactive estradiol and analyzed for receptor by IEF. The results were compared with those obtained by the DCC method on the same tumor. In 88% of the specimens examined both methods agreed as to the presence or absence of REc. A correlation coefficient, of 0.62 was calculated from the 15 positive results. There was no significant difference between the results from the two methods. Quantitative results were related to total protein concentration in the cytosol. Negative receptor status was defined as less than 5 fmol/mg protein for both methods. (2 Refs)

68. A FLUORESCENT METHOD OF MEASURING ESTROGEN RECEPTORS IN CYTOLOGIC MATERIAL (MEETING ABSTRACT).

Curtin CT, Pertschuk LP, Mitchell V
Moses Taylor Hospital, Scranton, PA
Acta Cytol (Baltimore); 25(4):450 1981

Biochemical methods of measuring estrogen receptors require 1 g of tissue and thus are not satisfactory for cytologic material. We report a histochemical test for measuring estrogen receptors at the cellular level. Fine needle aspirations were performed on 19 ptients with primary or metastatic mammary carcinoma. Representative aspirates were smeared on slides, and the diagnosis was confirmed. Parallel slides were transported on dry ice. Each smear was overlaid with 50 pmol of fluorescienated estradiol-bovine serum albumin ligand conjugate at room temperature for two hr. Parallel slides were exposed to a 100-fold M excess of antiestrogen C1-628. Smears were studied by incident UV light, and percentages of cells exhibiting nuclear, nucleolar and/or cytoplasmic binding were ascertained and graded for intensity of staining from 0 to + + +. Successful competition was determined by the presence of significantly less fluorescence in smears exposed to C1-628. Sixteen of 19 patients had biochemical determinations for comparison. Seven patients were receptor positive; six were negative using both determinations. Three cases were weakly positive biochemically and negative by histochemistry. In one of the discrepant cases, the biochemical test was performed two yr previously. In the other two cases, cellular primary tumors may have falsely elevated the biochemical test. (no Refs)

69. EFFECTS OF SODIUM MOLYBDATE ON STABLIZATION OF STEROID HORMONE RECEPTORS IN HUMAN BREAST CANCER (MEETING ABSTRACT).

Wong WH
CLMG Clinical Laboratory, Los Angeles, CA, 90057
Clin Chem; 27(6):1078 1981

Effects of the addition of sodium molybdate during the determinations of steroid hormone receptors were assessed for various final concentrations of molybdate and at various temperatures. Estrogen, progesterone, androgen and glucocorticoid receptors were determined in human breast cancer cytosols by dextran-coated charcoal method, with and without addition of sodium molybdate. Results indicated that with the presence of at least 20 mmol/L of molybdate, there was reduction in binding loss when incubated at all the temperatures tested. Significant increases in binding capacity were observed for progesterone and glucocorticoid receptors in some cytosols. Somewhat less increases were also observed for estrogen and androgen receptors in many cytosols. The number of receptor-positive specimens was increased while no specimen was observed to revert from positive to negative after addition of molybdate. Multiple determinations on pooled specimens also yielded better reproducibility of results with the presence of molybdate. We conclude that the addition of sodium molybdate does have a definitely positive stabilizing effect during the incubation of cytosol receptors with radio-labelled steroids. The inclusion of molybdate may be the next step towards the formulation of a standard method for the determination of steroid hormone receptors. (no Refs)

70. FREQUENCY OF 1,25-DIHYDROXYVITAMIN D3 RECEPTOR IN HUMAN BREAST CANCER.

Eisman JA, Suva LJ, Sher E, Pearce PJ, Funder JW, Martin TJ
Univ. Melbourne Dept. Medicine, Repatriation General Hosp., Heidelberg, 3081, Australia
Cancer Res; 41(12):5121-5124 1981

Receptors for 1,25-dihydroxyvitamin D3 have been shown to exist in cultured breast cancer cells and in primary breast cancers. It is reported here that 1,25-dihydroxyvitamin D3 receptor (1,25-DR) was present in 80% of 54 unselected breast cancers. The concentration of 1,25-DR in the 43 receptor-positive tumors was 1.9 +-0.4 fmol/mg protein (SE). There was no correlation between 1,25-DR presence or concentration and the age of the patient or the concentration of estrogen, progesterone, androgen, or glucocorticoid receptors. 1-25-DR was also found in two of three renal cortical carcinomas but only in 3 of 14 gastrointestinal tract carcinomas. The relatively low concentration of 1,25-DR in these breast cancers, compared with that found in cultured breast cancer cells, is partially explained by incomplete 'exchange' with occupied receptors. Since the serum vitamin D-binding protein is not precipitated from serum itself or from tissue homogenates using the polyethylene glycol method, artifactual 1,25-DR levels due to the inevitable contamination of tissue specimens with this protein can be excluded. These findings indicate that 1,25-DR is not a nonspecific marker of cancer. The high frequency of 1,25-DR in the breast cancers may be related to the calcium-transporting ability of breast cancer cells which allows them to grow as osteolytic metastases. (Author abstract) (23 Refs)

71. INFILTRATING LOBULAR CARCINOMA OF THE BREAST IN A PHENOTYPIC MALE (MEETING ABSTRACT).

Garcia Sanchez A, Redondo C, Alvarez I, Garcia Villanueva A, Ferrando P
Department of Pathological Anatomy, Genetics and Surgery, Centro Especial 'Ramon y Cajal', Madrid, Spain
Eighth European Congress of Pathology, August 30-September 4, 1981, Helsinki, Finland. 92 pp., 1981.

A case of bilateral breast carcinoma in a phenotypic male is presented. The left breast contained an infiltrating ductal carcinoma; the right breast contained an infiltrating lobular carcinoma with areas of 'in situ' lobular carcinoma and atypical lobular hyperplasia. These findings led us to perform the karyotype on the patient who was found to be a Klinefelter mosaic. Estrogen receptors were raised in both breast tumors, being higher in the lobular carcinoma. We performed also electron microscopy study in both tumors; the results are presented and compared. (no Refs)

72. BREAST TUMORS IN MALE DOGS.

Schonbauer M
Institut fur Pathologie und Gerichtliche Veterinarmedizin, Vet. Med. Universitat, Linke Bahngasse 11, A-1030 Vienna, Austria
Berl Muench Tieraerztl Wochenschr; 94(16):319-321 1981

Surgery of breast tumors was performed in 2,421 dogs during the period 1965-1979. Male dogs accounted for 23/2,421 (0.95%); this frequency is similar to that of breast cancer in men. The av age of the male dogs was 9.3 yr (2-14 yr), that of the bitches 8.9 yr. Benign mixed tumors were diagnosed in eight cases, tubular adenoma in four, solid adenoma in one, cystic adenoma in one, solid adenocarcinoma in one, tubular adenocarcinoma in two, papillary adenocarcinoma in three, cystic adenocarcinoma in one, anaplastic giant-cell carcinoma in one, and muciparous carcinoma in one. Testicular seminoma was also found in one dog. The tumors were histologically similar to those seen in the bitches. A relationship between breast tumors and gynecomastia vera in male dogs is not unlikely. (13 Refs) (In GER)

73. A DILUTIONAL IMMUNOPEROXIDASE STUDY OF PROLIFERATIVE DUCTAL LESIONS AND CARCINOMATA OF THE BREAST.

Wells S, Hasleton PS
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Histopathology; 5(5):517-526 1981

A dilutional immunoperoxidase technic using antiserum against carcinoembryonic antigen (CEA) was used to differentiate cases of epitheliosis, in situ and infiltrating ductal carcinoma, and in situ and infiltrating lobular carcinomas of the breast. In most of the cases of mild epitheliosis, the highest dilution of glycocalyceal staining was 1/400 and intraluminal staining 1/800. In cases of severe epitheliosis, intracytoplasmic staining, when present, was seen at dilutions of up to 1/400. Adjacent normal acini showed prominent glycocalyceal staining. In intraduct carcinoma cases, with cribriform/clinging patterns, positive staining was present in the following ranges: intracytoplasmic 1/100-1/5,000, glycocalyceal 1/800-1/5,000, and intraluminal 1/200-1/25,600. In all the cases of intraduct carcinoma with cribriform/clinging pattern and solid pattern with infiltration, the intraduct component stained at lower dilutions than the cases of pure intraduct carcinoma. Intraluminal staining was present in lower concentrations in the infiltrating component when compared with the intraduct part of the tumor. Intracytoplasmic staining was seen in the infiltrating component in some cases. In some cases of in situ lobular carcinoma with infiltration, intraluminal staining was noted in foci of adenosis and epitheliosis adjacent to lobular carcinoma. However, the normal breast tissue adjacent to the tumors did not usually stain positively at dilutions greater than 1/50. Results indicated that the dilutional immunoperoxidase technic for CEA appears useful in differentiating cases of severe epitheliosis from cribriform/clinging pattern of intraduct carcinoma. (12 Refs)

74. ABNORMAL NIPPLE ASPIRATE CYTOLOGY AND PROLIFERATIVE CHANGES IN BENIGN BREAST DIS EASE (MEETING ABSTRACT).

King EB, Chew K, Barrett DL, Ernster V, Petrakis NL
University of California School of Medicine, San Francisco, CA
Acta Cytol (Baltimore); 25(4):450 1981

Abnormal nipple aspirate cytology is found with increased frequency in women with breast cancer risk factors, such as benign breast disease. The purpose of this report is to describe an anatomic basis that we have found for the significance of abnormal cells in these women. Nipple secretions and subsequent benign breast biopsies from 232 women were examined. Duct epithelial cells were classified as normal or as cells representing a duct epithelial proliferative process. The latter constituted a continuum of increasing abnormality, to which the terms hyperplasia, atypical hyperplasia and dysplasia were applied. The duct epithelium in the breast tissue from biopsy was reviewed independently and classified using the same terminology used for the aspirate samples. We found a significant association between ductal atypia in the nipple aspirate and breast tissue specimens: women with abnormal cytology were more likely than women with benign cellular findings to have a histologic diagnosis of proliferative disease with atypia. These results confirm the anatomic basis of abnormal cytology in our study of breast cancer risk factors, although the cytologic results were not sufficiently predictive to be used for diagnostic purposes. (no Refs)

75. INTRACELLULAR CONTENT OF SODIUM AND OTHER ELEMENTS AS RELATED TO THE CONTROL OF PROLIFERATION OF NORMAL AND TRANSFORMED CELLS.

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The University of Texas Health Science Center at San Antonio, San Antonio, TX
Diss Abstr Int [B]; 42(3):881-B 1981

Significantly higher intracellular levels of Na were found in both the H6 hepatoma and the 13762 NF mammary adenocarcinoma as compared to their normal counterpart cells in vivo. Amiloride, a drug known to block passive Na+ influx, was shown to inhibit H6 hepatoma and DMA/J mammary adenocarcinoma growth in vivo and to inhibit H6 cell and DMA/J cell proliferation in vitro. Treatment of animals bearing an H6 hepatoma with amiloride caused a decrease in intracellular Na, but not in a dose-dependent manner. In fact, the group receiving the lowest dosage of amiloride had the lowest levels of intracellular Na, but tumor growth had not been significantly inhibited at that dosage. Thus, the intracellular level of Na was not directly related to tumor growth. This would suggest that high intracellular levels of Na are related to oncogenesis, but may be a result of the cancer lesion(s) rather than a cause. In accordance with current findings published in the literature, Na+/influx may play a greater role in the regulation of cell proliferation than does its intracellular concentration. Therefore, it may be that amiloride inhibited proli feration of the different cell types due to its inhibition of Na+ influx. (no Refs)

76. EXPRESSION OF TUMOR SPECIFIC PROPERTIES BY HUMAN MAMMARY EPITHELIUM IN CULTURE (MEETING ABSTRACT).

Stampfer MR, Hackett AJ, Bartley J, Leung JP, Edgington TS, Smith HS
Lawrence Berkeley Lab., Berkeley, CA
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Our laboratory has developed a culture system for studying carcinogenesis and expression of differentiated properties of human mammary epithelium. We can now readily culture over 90% of specimens representing various stages of malignant progression including reduction mammoplasties, peripheral mastectomy tissue, primary carcinomas, and hypodermal metastases. The mammary tissue can be enzymatically digested to pure epithelial clusters, which may be cryopreserved in multiple ampoules, permitting repetition of experiments with cells from individual donors. Utilizing an enriched medium plus cholera toxin, the epithelial cells can be grown in mass culture with doubling x of 24-48 hr and can be subcultured 1-3 x at 10-fold dilution. By plating on irradiated fibroblasts in the enriched medium, single epithelial cells develop into colonies with plating efficiencies ranging from 6-40%. The cells are identified as epithelial by electron microscopy, presence of domes, a distinctive pattern of fibronectin distribution and the presence of human mammary epithelial antigen. To elucidate the nature of the malignant transformation, we have begun to compare the properties in culture of the normal and malignant cells. While we have found that cells derived from both normal tissues and primary carcinomas display similar patterns of cellular fibronectin distribution and secretion, all of the six tumor derived specimens examined thus far express a membrane associated glycoprotein (MTGP-20) not found on any of the non-tumor derived specimens examined. (1 Ref)

77. HUMAN MAMMARY EPITHELIUM IN CULTURE (MEETING ABSTRACT).

Smith HS, Hackett AJ, Ceriani R, Stampfer MR
Peralta Cancer Research Institute, Berkeley, CA, 94720
In Vitro; 17(3):203 1981

Our laboratory has developed a culture system for studying carcinogenesis of human mammary epithelium. We can now readily culture over 90% of specimens representing various stages of malignant progression including reduction mammoplasties, peripheral mastectomy tissue, primary carcinomas, and hypodermal metastases. Briefly, mammary tissue is enzymatically dissociated from stromal elements, separated by filtration and cryopreserved. Utilizing an enriched media plus cholera toxin, the epithelial cells can be grown in mass culture with doubling x of 24-48 hr and can be subcultured approx 1-4 x at a 10 fold dilution. By plating on irradiated fibroblasts in enriched media, single epithelial cells develop into colonies with plating efficiencies ranging from 6-40%. The cells are identified as epithelial by electron microscopy, by the presence of domes and ridges, by a distinctive abbreviated fibronectin pattern and by the presence of mammary epithelial antigen. To elucidate the nature of malignant transformation, we have begun to compare the properties in culture of the normal and malignant cells. There are subtle differences in morphology with the most notable being an increased nuclear:cytoplasmic ratio in the tumor cells. The tumor and normal cells also differ in colony morphology. The normal cells form an organized noninvasive colony while the malignant specimens contain a population of colony forming cells that invade the stromal feeder layer. (1 Ref)

78. ULTRASTRUCTURAL OBSERVATIONS ON BREAST CANCER CELLS AND ON THEIR MITOCHONDRIA IN PLEURAL EFFUSIONS AND IN TISSUE CULTURE (MEETING ABSTRACT).

Seman G, Lukeman JM, Cailleau R, Edwards C
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
In Vitro; 17(3):225 1981

Studies were initiated on the significance of rod-like inclusions previously observed by electron microscopy in mitochondria of epithelial cells in about 40% of breast cancer biopsies examined in our laboratory. Rods were found in cells of one fresh pleural effusion out of 6. No rods were observed in cells of 5 tissue cultures established from pleural effusions (MDA-MB 157, 435, 436, 453 and 469) grown the usual way in shallow medium. However, upon growth in stoppered plastic (Corning T 25) or glass flasks filled up with medium rods appeared in MB-435 and-453 cells grown in plastic flasks. The rods do not appear to derive from mitochondrial cristae and structurally resemble the enzyme glutamate dehydrogenase. The reasons for rod formation are not yet known. Lack or excess of l-glutamine in medium did not elicit them in MB-435 cells. Unlike cells from the three other lines, MB-435 and-453 cells did not contain duct-like vacuoles often claimed to be typical of breast cancer cells grown in vitro. Thus cell lines established from pleural effusions may be derived from at least two different types of cells (glandular versus ductal or ductular?) differing in their structure and in the behavior of their mitochondria under specific growth conditions. (no Refs)

79. COMPARISON OF CEA POSITIVITY AND NUCLEAR DNA-DISTRIBUTION IN MAMMARY CARCINOMAS (MEETING ABSTRACT).

Wittekind C, Von Kleist S, Guzman J, Kiefer G
University of Freiburg, Freiburg, W. Germany
Oncodev Biol Med; Abstracts Book,1:26 1981

Nuclear DNA estimation has been postulated to be a helpful parameter in the evaluation of malignant potential of many carcinomas. A correlation between DNA distribution and estrogen receptor status has been demonstrated in mammary carcinomas in the sense that carcinomas with high degrees of aneuploidy have very low estrogen receptor levels. It was investigated in this study whether a particular DNA pattern could be attributed to the ability of mammary carcinoma cells to produce and/or secrete CEA. Furthermore we looked into the question if the DNA distribution signalled any malignant potential of the tumor cells. Fifty invasive mammary carcinomas, classified according to World Health Organization were studied for their DNA distribution pattern and for the presence of serum and tissue CEA, using the immunoperoxidase technique. These data were correlated with axillary lymph node metastases. When only presence and absence of tissue CEA were considered, there was no obvious correlation between the type of DNA-profile, CEA positivity and the presence of axillary lymph node metastases. However, mammary carcinomas with near-diploid or near-tetraploid DNA values showed significantly more often elevated serum levels than carcinomas with triploid or hypotetraploid DNA values. Therefore, we suggest that the latter carcinomas have lost the ability to secrete the produced CEA in the serum. (no Refs)

80. BASEMENT MEMBRANE CHANGES IN BREAST CANCER DETECTED BY IMMUNOHISTOCHEMICAL STAINING FOR LAMININ.

Albrechtsen R, Nielsen M, Wewer U, Engvall E, Ruoslahti E
Univ. Inst. Pathological Anatomy, Frederik V's vej 11, DK-2100 Copenhagen, Denmark
Cancer Res; 41(12):5076-5081 1981

The distribution of the basement membrane glycoprotein laminin was studied by the immunoperoxidase technique in benign and malignant human breast tissue and in axillary lymph nodes from patients with breast cancer. An antiserum prepared against rat laminin was used. The specificity of this antiserum against laminin was studied using the FL cell line of human epithelial-like cells derived from normal amniotic membrane. The antiserum reacted with these cells in immunoperoxidase staining and precipitated metabolically labeled secreted polypeptides which comigrated with polypeptides with mol wt of 400,000 and 200,000 of rat laminin in sodium dodecyl sulfate:polyacrylamide gel electrophoresis. The neoplastic cells in malignant breast tissues showed strong cytoplasmic staining for laminin, and a positive reaction was also found in lymph node metastases. In some cases in which only micrometastases were present, these cells also stained strongly for laminin. In nonmalignant breast tissues, the epithelial cells of the ducts were positive for laminin, but the staining was weaker than in the carcinomas. Pretreatment of the fixed tissue sections with trypsin markedly enhanced the staining of basement membranes for laminin. In trypsin-treated sections of normal breast tissue and benign lesions, the laminin staining delineated continuous basement membranes. In carcinomas representing the more differentiated types, basement membranes presumably produced by the tumor cells could be revealed by laminin staining, but they were thinner and discontinuous. The poorly differentiated carcinomas lacked organized basement membranes detectable by laminin staining. Our studies suggest that staining for laminin may be a useful adjunct test for detection of micrometastases in lymph nodes. The correlation of disintegration of the laminin-containing basement membranes of tumors with increasingly anaplastic appearance supports the notion that basement membranes may play a role in tumor invasion. (Author abstract) (33 Refs)

81. LAMININ IN BASEMENT MEMBRANES OF A RAT YOLK SAC CARCINOMA AND HUMAN CARCINOMAS (MEETING ABSTRACT).

Wewer U, Albrechtsen R, Engvall E, Ruoslahti E
La Jolla Cancer Research Foundation, 2945 Science Park Road, La Jolla, CA, 92037
Oncodev Biol Med; AbstractsBook,1:P16 1981

Laminin, a non-collagenous component of basement membranes, has recently been identified in the mouse. We have induced a rat yolk sac carcinoma with abundant hyalin material, a main part of which was found to be laminin. The human counterpart of rodent yolk sac carcinoma, the endodermal sinus tumor, was investigated for the presence of laminin with an immunohistochemical staining method. Areas with hyalin material were markedly positive for laminin, indicating that the matrix secreted by the tumor cells is composed of basement membrane material. The presence of laminin in other human carcinomas was further investigated in breast tissues. Epithelial cells of normal ducts and neoplastic cells, including metastatic cells, showed positive cytoplasmic staining for laminin. Single tumor cells could be detected by laminin staining in axillary lymph nodes. Laminin staining delineated continuous basement membranes in benign breast lesions while in carcinomas these were discontinuous or absent. The correlation of disintegration of the laminin-containing basement membranes of the tumors with increasingly anaplastic appearance supports the notion that basement membranes may play a role in tumor invasion. (no Refs)

82. THE DISTRIBUTION OF KERATIN TYPE INTERMEDIATE FILAMENTS IN HUMAN BREAST CANCER: AN IMMUNOHISTOLOGICAL STUDY.

Altmannsberger M, Osborn M, Holscher A, Schauer A, Weber K
Dept. Pathology, Univ. Gottingen, D-3400 Gottingen, W. Germany
Virchows Arch [Cell Pathol]; 37(3):277-284 1981

Antibodies to different intermediate filament proteins can be used to distinguish cells of epithelial, mesenchymal, muscle, glial and neuronal origin. Antibodies to prekeratin which characterize cells of epithelial origin, and antibodies to vimentin which recognize cells of mesenchymal origin have been used to study 20 cases of breast carcinoma (16 infiltrating ductal carcinomas and 4 infiltrating intraductal carcinomas), 2 cases of cystic breast disease, 2 fibroadenomas and 1 case of benign cystosarcoma phylloides. The prekeratin and vimentin were detected using specific antibodies to these proteins by immunofluorescence microscopy using alcohol fixed paraffin-embedded tissues. In eighteen out of the 20 carcinomas the tumor cells were strongly and specifically stained by antibodies to prekeratin. Different tumors gave different patterns of prekeratin staining. In contrast, when the same specimens were tested with the vimentin antibody, the tumor cells were unstained, and instead only the usual strong staining to fibroblasts and blood vessels in the stroma was observed. In cystic breast disease, fibroadenomas, and benign cystosarcoma phylloides, cells of epithelial origin were strongly stained by the prekeratin but not by the vimentin antibody. (Author abstract) (21 Refs)

83. DIFFERENTIATION OF HUMAN BREAST CARCINOMAS: AN IMMUNOHISTOLOGICAL STUDY OF APPROPRIATE AND INAPPROPRIATE PROTEIN PRODUCTION.

Walker RA
Dept. Pathology, Univ. Leicester, P. O. Box 65, Leicester LE2 7LX, England
J Pathol; 135(1):87-95 1981

A series of breast carcinomas was analyzed by an indirect immunoperoxidase method for evidence of production of secretory piece and beta1 pregnancy-specific glycoprotein (BPSG). Results were examined with respect to histologic differentiation and structure. Secretory piece of immunoglobulin A could be demonstrated in 29/75 carcinomas and BPSG in 28/75 tumors. No staining was evident in control sections treated with normal rabbit serum. Staining was abolished in breast carcinoma cells after absorption of anti-BPSG serum by 1.8 ug BPSG. No staining of the cells of normal breast ducts of acini occurred. More negative than positive cells were found in the section examined for both antigens. Seven of the carcinomas in which secretory piece was demonstrated had staining either in three to five discrete areas, or as single or small groups of cells in a diffuse pattern throughout the section. The other 22 tumors showed staining in one or two areas only. Findings were similar for BPSG, with 22 carcinomas having a small number of positive cells and six tumors a greater number. Poorly differentiated carcinomas had a low incidence of detection for both antigens. Well-differentiated tumors were heterogeneous in protein staining. (12 Refs)

84. ECTOPIC PRODUCTION OF ONCODEVELOPMENTAL PROTEINS BY BREAST CANCERS (MEETING ABSTRACT).

Horne CH, Bremner RD, Nisbet AD, Bohn H, Ratcliffe JG
Department of Pathology, University of Aberdeen, Aberdeen, Scotland
Oncodev Biol Med; AbstractsBook,1:P66 1981

Using an indirect immunoperoxidase technique and specific sensitive radioimmunoassays a series of breast cancers sent to this laboratory for routine frozen section diagnosis have been screened for the presence of pregnancy-specific glycoprotein (SP1), placental protein five (PP5) and carcinoembryonic antigen (CEA). In addition the occurrence of these oncodevelopmental proteins has been compared with the presence or absence of estrogen receptors. (no Refs)

85. CYCLIC AMP-BINDING PROTEINS IN HUMAN MCF-7 CELLS AND BREAST CANCER (MEETING ABSTRACT).

Eppenberger U, Handloser K, Kung W, Handschin J
Department of Research and Gynecology, University Medical School, 4031 Basel, Switzerland
Oncodev Biol Med; Abstracts Book,1:54 1981

Several recent investigations have indicated that a relationship exists between intracellular levels of cyclicAMP (cAMP) and cAMP-dependent protein kinase isozymes Type I and Type II during normal and neoplastic growth. This study demonstrates a significant alteration in the cAMP-binding protein pattern (regulatory subunit R-II of Type II) of human neoplastic mammary tissue and human mammary MCF-7 cells as compared to normal and dysplastic mammary tissues. Fotoaffinity labeling of the cAMP receptors with 8-N3 [32P] cyclic AMP revealed on sodium dodecyl sulfate polyacrylamide gels 3 cAMP-binding proteins of R-II and a cAMP-binding protein apparent mol wt of 40,000, which could not be detected in normal and dysplastic mammary cells. It is suggested that the 40,000 mol wt protein results from a limited proteolysis. Only small amounts of the regulatory subunit R-I of isozyme Type I were observed in MCF-7 cells and breast cancer tissue, whereas in normal mammary tissue no R-I could be found. It is suggested that the cAMP-binding protein of 40,000 mol wt has some prognostic value with respect to endocrine therapy of breast cancer. (no Refs)

86. A PRELIMINARY STUDY OF THE CREATINE KINASE BB ISOENZYME AS A TUMOR MARKER (MEETING ABSTRACT).

Fritsche HA, Wertlake SE

Department of Laboratory Medicine, University of Texas System Cancer Center, M. D. Anderson, Hospital Houston, TX, 77030

Oncodev Biol Med; Abstracts Book,1:P15 1981

We have used a radioimmunoassay (RIA) procedure to measure the BB isoenzyme of Creatine Kinase (CK-BB) in the serum of patients with cancer. The normal range for the assay was established in a study of 170 blood donors. The upper limit of normal for CK-BB was 8.0 ng/ml and no effect of age or sex on the normal range was observed. Serum CK-BB levels were determined in 355 cancer patients with a variety of neoplastic diseases who were in various stages of their disease. Serum CK-BB elevations were frequently observed in patients with adenocarcinoma of the gastrointestinal (GI) tract, breast and prostate. Approx 50% (10/24) of the patients with GI tract malignancy undergoing therapy and 30% (6/18) patients with breast cancer had elevated serum CK-BB levels. Elevations of CK-BB in patients with prostate cancer appeared to correlate with the presence of metastatic bone disease. CK-BB elevations by RIA were confirmed by electrophoretic studies. Serial determinations of CK-BB in patients undergoing therapy correlated with the clinical response to therapy and elevations of serum CK-BB in disease free patients signaled recurrence of the disease. Borderline elevations of CK-BB (8.0-10.0 ng/ml) were observed in some cancer patients with renal failure and drug induced cardio-toxicity. These preliminary studies suggest that the CK-BB test may be useful in the clinical management of patients with cancer. (no Refs)

87. STUDIES ON SIALYLTRANSFERASE ISOENZYMES IN PLASMA OF PATIENTS WITH BREAST CANCER.

Kessel DH, Chou TH, Coombes RC

Dept. Oncology, Harper Hosp., Detroit, MI, 48201

Eur J Cancer Clin Oncol; 17(9):1035-1040 1981

An elevated level of sialyltransferase was often found in plasma of patients with breast cancer, but the extent of this elevation was highly variable, as was the enzyme level in plasma of normal donors. Electrofocusing studies indicated the presence of sialyltransferases, focusing at pH 5.2 and 5.6, in all plasmas examined. Elevated enzyme activity in plasma of normal donors was associated with appearance of an 'inflammatory response' isoenzyme with $pI = 7.5$. In plasma of the individuals with untreated primary or recurrent breast cancer, we found a new sialyltransferase isoenzyme with $pI = 4.7$. This isoenzyme was not detected in plasma of patients with benign breast disease. (Author abstract) (19 Refs)

88. PARTIAL PURIFICATION OF MAMMARY TUMOR CELL ESTROMEDINS FROM PREGNANT SHEEP UTERUS (MEETING ABSTRACT).

Iio M, Sirbasku DA

Department of Life Sciences, Kumamoto Women's University, Kumamoto, Japan

Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

We have proposed that one role of estrogens may be to regulate the production of protein mediators (estromedins) which function as primary mitogens in vivo. Experiments have shown that uterus and kidney of the rat are rich sources of estrogen-induced activities for the MTW9/PL, T47-D and MCF-7 mammary tumor cells. Partial purification of the mitogen(s) has been conducted, but this source of growth factor has proven inadequate for large scale preparations of mammary cell estromedins, especially in view of our interest in obtaining amounts sufficient for sequence and mechanism studies. We have sought larger scale sources of mammary cell estromedins and found that pregnant sheep uterus provided a high specific activity source. There appear to be two separable activities in sheep uterus, both of which are mitogenic for MTW9/PL rat mammary cells, and which appear to act synergistically to account for the total uterine derived estromedin activity. (no Refs)

89. INDUCTION OF ORNITHINE DECARBOXYLASE IN CULTURED MAMMARY TUMOR CELLS (MEETING ABSTRACT).

Cohen LA, Van der Snoek L

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In Vitro; 17(3):242 1981

At present, little is known concerning the role played by polyamines in mammary cancer. Since in vivo studies are difficult to interpret at the cellular level, we have developed a defined in vitro system consisting of neoplastic epithelial cells derived from an N-nitrosomethylurea induced rat mammary adenocarcinoma. Ornithine decarboxylase (ODC), the rate-limiting step in polyamine synthesis, was measured in these cells by the in situ method of Patterson and Maxwell. To induce ODC, late log-phase cells were grown in serum-depleted medium. The kinetics of ODC induction was similar to that reported in other cell lines. Specific activity (sp act) at 0, 15 and 60 min was less than 0.5, 3.25 and 6.30 nmoles carbon dioxide/mg prot/hr, respectively; between 1 and 2 hr little change in sp act was observed. The specificity of the reaction was assessed by addition of inhibitors of the reaction mixture for the 2 hr assay period. There was an absolute requirement for pyridoxal phosphate; the reaction product, putrescine, inhibited ODC in a logarithmic fashion, and the competitive inhibitor alpha-methylornithine reduced enzyme activity by half. (1 Ref)

90. PEROXIDASE ACTIVITY IN MAMMARY TUMORS - EFFECT OF TAMOXIFEN.

Levy J, Liel Y, Feldman B, Aflallo L, Glick SM

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Eur J Cancer Clin Oncol; 17(9):1023-1026 1981

Dimethylbenz(a)anthracene (DMBA)-induced tumors in rats were studied for changes in size, cytosolic estrogen (ER) and progesterone (PgR) receptors, and for peroxidase activity before treatment, after 15 days of treatment with the anti-estrogen tamoxifen, and 15 days following cessation of the treatment. Mean size of the tumors decreased significantly during the treatment period to 1/3 the original size and ER and PgR decreased significantly to 1/5 their original levels. Peroxidase activity increased 30-fold. All the changes reversed significantly 15 days after cessation of tamoxifen treatment. These results are consistent with a previous study in which regression of the tumors was induced by castration and recovery was brought about by treatment with estradiol. In DMBA-induced mammary tumors in rats, peroxidase activity in regressing and growing tumors is in inverse relation to changes in tumor size, ER and PgR, which are accepted indicators of estrogenic activity. (Author abstract) (16 Refs)

91. DEMONSTRATION OF PREGNANCY-ASSOCIATED ALPHA2-GLYCOPROTEIN (ALPHA2-PAG) IN PREGNANT, ESTROGEN-TREATED AND BREAST CANCER-BEARING RATS.

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Oncodev Biol Med; 2(5):345-354 1981

A high mol wt (382,000 daltons) pregnancy-associated alpha alpha2-glycoprotein (A-PAG) was detected in the sera of pregnant, estrogen-treated, and breast cancer-bearing female Sprague Dawley rats. Double immunodiffusion patterns gave immunologic reactions of identity. A-PAG was not detected in the serum of either normal or injured adult female or male rats. The relative concentrations of A-PAG measured in pregnant rats by rocket immunoelectrophoresis increased rapidly and progressively, and reached a max during the third trimester of gestation then decreased to undetectable levels within 3 days postpartum. The serum concentrations of A-PAG in estrogen-treated female rats also reached a max level equal to that found in pregnant rats. The evidence presented here indicates that this high mol wt pregnancy-associated alpha2-glycoprotein is analogous to its human counterpart, and that this animal model system is suitable to study sites of synthesis, and the biologic function of this protein. (36 Refs)

92. DIFFERENTIATION IN CULTURE OF A RAT MAMMARY STEM CELL LINE (MEETING ABSTRACT).

Rudland PS, Warburton MJ

Ludwig Institute, Royal Marsden Hospital, London, England

International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Three main types of mammary epithelial cells are distinguishable in normal mature glands and in carcinogen induced tumors, those lining the alveoli, those lining the ducts and the myoepithelial cells round both ducts and alveoli. We have previously isolated a clonal epithelial stem cell line from a dimethylbenz(a)anthracene-induced rat mammary carcinoma which can give rise to both alveolar-like and myoepithelial-like cells in culture. The former process can be accelerated by a combination of dimethyl sulphoxide (DMSO) and the mammotropic hormones, prolactin, hydrocortisone and insulin. We now report that the artificial inducer DMSO can be replaced by prostaglandin (PG)E1 and to a lesser extent by PGE2 and PGF2alpha in accelerating this differentiation step. The alveolar-like cells also produce fewer tumors than their parent cells when injected into immunodeprived (nu-nu) mice. Thus this process of differentiation which can be regulated in part by PGE1 in vitro is also accompanied by a reduction in neoplastic potential when the cells are tested in vivo (no Refs)

93. MORPHOLOGIC CHARACTERISTICS OF PREGNANCY-DEPENDENT MAMMARY TUMORS IN GRS/A MICE.

Tsubura A, Morii S

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Gan; 72(5):639-646 1981

Groups of pregnancy-dependent mammary tumors from GRS/A female mice, composed of early, maximally grown and regressed tumors, were investigated morphologically in comparison with functionally active normal mammary gland of the same host and pregnancy-independent mammary tumors of the same strain. In the dependent tumors, earlier ones consisted of proliferating, non-secretory ductular cells in loose stroma, which grotesquely resembled normal mammary gland architecture, and the maximally grown feature was the localized overgrowth of the ductal lobular unit, in which papillomatous proliferations of ductal structures were observed. Histochemically, few myoepithelial cells in the tumors, low secretory activity and poor expression of murine mammary tumor virus antigens in these tumor cells were detected, as contrasted with neighboring mammary glands of pregnant and lactating mice. Particularly severe necrosis occurred in the papillomatous foci of ductal elements within the dependent tumors soon after parturition, and these finally changed to a group of microcysts. Small foci of adenocarcinoma Type B were rarely seen in the dependent tumors during later pregnancies, and some cancer cells showed an intracytoplasmic focal staining for the viral antigens. Such an immunohistochemical finding was never detected in the dependent tumors. (Author abstract) (18 Refs)

REVIEWS AND OTHER RELATED STUDIES

94. CANCER RISKS OF MEDICAL TREATMENT. PART II: POTENTIALLY CARCINOGENIC MEDICATIONS IN CURRENT USE.

Schottenfeld D

Dept. Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

Clin Bull; 11(2):75-82 1981

Experimental and epidemiological data on the carcinogenicity of currently available drugs are reviewed. Patients treated with cytotoxic antineoplastic agents are at increased risk for bladder cancer and acute nonlymphocytic leukemia. Immunosuppressive agents are associated with development of lymphoreticular malignancies in renal transplant recipients. Estrogen administration increases the risk of endometrial and breast carcinoma in menopausal and postmenopausal women. Oral contraceptives have been shown to be associated with endometrial cancer, uterine cervical dysplasia, and cervical carcinoma in situ. Oral contraceptives reduce the risk of benign breast diseases. Androgenic anabolic steroids have been found to cause liver carcinoma. Methoxypsoralen in the presence of UV increases the risk of skin carcinoma. Phenacetin-containing analgesics have been shown to cause chronic interstitial nephritis, carcinoma of the renal pelvis, and bladder carcinoma. Potentially carcinogenic but cost-effective drugs should be prescribed at the lowest dose and for the shortest period of time. (59 Refs)

95. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL
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Epidemiol Rev; 3:184-202 1981

Epidemiology of benign breast disease (BBD) is reviewed. Topics include BBD (the problem of case definition), estimates of the occurrence of BBD, evidence for an association of BBD and breast cancer, interaction of BBD and other risk factors for breast cancer, and factors associated with BBD (age, race, socioeconomic status, menstrual and reproductive characteristics, family history of breast cancer, obesity, endogenous hormone levels, and exogenous hormone use). Published data for the occurrence of BBD, risk of breast cancer associated with BBD, relative risk of breast cancer associated with various factors among women with and without BBD, menstrual and reproductive factors in relation to BBD, and biopsy-defined BBD and oral contraceptive use are summarized. Evidence suggests that risk of breast cancer associated with various factors may be greater in women with BBD than in those with no such history; inconsistencies across epidemiologic studies may result from a lack of analyses specific to histopathologic type of benign disease. (79 Refs)

96. ONCOGENIC VIRUSES.

Wyke JA
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J Pathol; 135(1):39-85 1981

Virus-induced cancer in animals, including man, and the molecular mechanisms of virus-induced neoplasia are reviewed. Topics discussed include the diversity of relationships between oncogenic viruses and host animals, the problem of identifying human tumor viruses, and a brief catalogue of clinically important oncogenic viruses (avian retroviruses, murine leukemia and sarcoma viruses, leukemia and sarcoma viruses of other species, mouse mammary tumor virus, retroviruses and nonneoplastic disease, papovaviruses, adenoviruses, lymphotropic herpesviruses, other herpesviruses, hepatitis B virus, and poxviruses). General features of the interactions between viruses and their host cells, the transformed cell, replication of retroviruses, and cell transformation and tumor formation by retroviruses are discussed. (85 Refs)

97. STRESS AND CANCER: THE STATE OF THE ART (PART 2).

Bahnson CB
Dept. Psychiatry, Jefferson Medical Coll., Philadelphia, PA, 19107
Psychosomatics; 22(3):207-209,213,217-220 1981

The relationship of specific personality patterns and ego defenses to cancer and possible intervening psycho-physiologic processes were examined. In a review of the literature evidence indicated that cancer patients rely heavily on denial and repression. Early family patterns which include inadequate affective communication and object relationships seem to impair the cancer patient's capacity for affective expression later in life. Several studies of breast cancer patients seem to support this loss-depression hypothesis. Three means by which these psychosomatic mechanisms may lead to cancer are presented. The neurologic pathway is examined using studies relating CNS changes and malignancy. Endocrine system 'bridges' between psychological states and cancer include changed hormone profiles, which may inhibit or stimulate the immune reaction. The immune system pathway is a third bridge to cancer. Clarification of the relationship between psychologic and physiologic variables in clinical cancer is needed. (79 Refs)

98. BREAST CANCER.

Arseneau JC
Rochester Univ. Sch. Medicine and Dentistry, Rochester, NY
Practical Cancer Chemotherapy. Rosenthal SN, and Bennett JM, ed. Garden City, NY, Medical Examination Publishing Co., 461 pp., 1981.

The etiology, clinical features, and treatment of malignant breast cancers are reviewed. The low incidence of breast cancer in women castrated in youth and in women who have early or multiple pregnancies implicates hormones as factors in etiology, although their role remains unclear. High-risk populations can be defined by exposure to environmental factors, such as ionizing radiation, or genetic factors such as a history of breast cancer in close female relatives. No conclusive evidence has yet linked viruses to human breast cancer. Most breast cancers are ductal type adenocarcinoma. Most lesions present as a painless mass, and signs of metastatic disease may be present either locally (enlarged lymph nodes in axilla, supraclavicular, or cervical areas) or at distant sites such as bone, liver, lung, or brain. Diagnosis of breast cancer is made by biopsy and microscopic examination of the biopsy specimen. A bone scan is often done to search for subclinical metastases. Surgical intervention is the method of choice in the initial management of malignant breast disease, with much current debate concerning particular procedures. In fact, variations in local therapy have little effect on survival. Hormonal and cytotoxic drug therapy is discussed. (44 Refs)

99. OVERVIEW: EPIDEMIOLOGICAL ASPECTS OF TUMOR PROMOTION (MEETING ABSTRACT).

Wynder EL
American Health Foundation, Valhalla, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The causes of the main human cancers, namely those in the respiratory tract, the gastro-intestinal tract, and the endocrine-sensitive organs, especially breast and prostate, are complex and multifactorial. A major risk factor for respiratory tract cancers is tobacco, containing genotoxic carcinogens but, importantly also, cocarcinogens and promoters of diverse kinds including phenolic compounds. Cancers of the colon, breast, and prostate involve as yet unknown carcinogens, possibly related to the intake of mutagens in fried foods. The major contributing effect for these types of cancer is related to the level of dietary fat consumed which, in turn, through endogenous metabolism, generates proportional levels of bile acids, shown to be promoters in colon cancer, and of specific endocrine balances which appear to play a promoting role in cancer of the breast and prostate. Inasmuch as promotion is highly dose-dependent and reversible, there is evidence that alteration of the promotion phase of carcinogenesis may rapidly and effectively establish a lower risk situation. Individuals who stop smoking remove the pressure of promotion progressively, thereby lowering their risk of lung cancer development. Individuals who consume food with higher cereal fiber or lower fat content decrease the effective concentration of bile acids and have reduced risk of colon cancer. In many instances, parallel confirmatory results have been obtained in animal models. Thus, there is hope that modulation of the promotion phases in specific promotion-dependent human carcinogenesis may permit a relatively rapid and effective reduction of risk. (no Refs)

100. MODEL FOR HUMAN CARCINOGENESIS: ACTION OF ENVIRONMENTAL AGENTS (MEETING ABSTRACT).

Moolgavkar SH
Institute for Cancer Research, Philadelphia, PA
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Current statistical prescriptions for low-dosage extrapolation of carcinogenic risk make no distinction between exposure to initiators and exposure to promoters despite the abundant data that these two classes of carcinogens have different modes of action. One reason for this is the lack of an appropriate model. In this paper, a model for carcinogenesis is presented which provides a framework for understanding the roles of 'spontaneous' events, hereditary factors, and environmental agents in human carcinogenesis and for interpreting experimental carcinogenesis. This model incorporates two features: (1) transition of target stem cells into cancer cells via an intermediate stage in two irreversible steps, (2) growth and differentiation of normal target and intermediate cells. Cast in mathematical terms the model can be fitted to age-specific incidence data on human cancers of both children and adults and can illuminate the relative importance of agents that affect transition rates, tissue growth and tissue differentiation. Within the context of the model, initiators act by affecting the transition rates, whereas promoters influence the kinetics of growth, especially of initiated cells. The model provides a good quantitative description of the epidemiology of carcinomas of the breast and of the lung. The data are consistent with the notion that hormones and cigarette smoke act as promoting agents in carcinoma of the breast and of the lung respectively. (no Refs)

101. OTHER IATROGENIC CANCERS (MEETING ABSTRACT).

Ross RK
No affiliation given
The Causes of Cancer, November 6, 1981, Los Angeles, California California Hospital Medical Center; 1981

The majority of iatrogenic cancers fit into two categories: those induced by diagnostic or therapeutic radiation and those induced by prescription drugs. Since radiation induced cancer has already been discussed in detail, this session will be primarily concerned with drugs as causes of human cancer. Several drugs which are now recognized as causes of human cancer have been detected only because of the rarity of the cancer in the absence of the drug. For example, the association between a mother's use of diethylstilbestrol during pregnancy and the development of clear cell adenocarcinomas of the vagina in her daughter decades later was only detected because several cases of this extremely rare tumor were noted in a single hospital in a rather short period of time. Similarly, in a case-control study at University of Southern California, it was demonstrated that risk to women or a rare form of liver cancer, benign liver adenoma, was strongly related to duration of use of oral contraceptives. It seems likely that such relationships exist for more common cancers by go undetected either because no one suspects this relationship or the relationship is difficult to study in the face of other factors causing the same disease. In fact, several such relationships with more common cancer sites have been demonstrated in recent yr. Use of amphetamines has been shown to increase one's risk to Hodgkin's disease some 4-6 fold, use of immunosuppressive drugs has been demonstrated to greatly increase risk to non-Hodkins' lymphomas and use of estrogen replacement therapy, perhaps the most widely studied group of drugs in terms of cancer risk, increases risk of endometrial cancer and breast cancer. (no Refs)

102. FACTORS THAT PROMOTE THE DEVELOPMENT OF HUMAN BREAST CANCER (MEETING ABSTRACT).

Thomas DB
Fred Hutchinson Cancer Research Center, Seattle, WA
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

The epidemiologic features of breast cancer and current hypotheses regarding the etiologic role of endogeneous hormones are summarized and evaluated. The inconsistent results of studies of exogenous hormones and breast cancer are also critically summarized. A proposed model for human mammary carcinogenesis is presented. Hormonal aberrations that vary with reproductive and menstrual events are hypothesized to alter susceptibility of mammary tissue to primary carcinogens. The nature of these aberrations, and the identity of the primary carcinogens are largely unknown. Avenues for further research are suggested. (no Refs)

103. THE RELATIONSHIP BETWEEN DIETARY FAT AND HORMONES IN MAMMARY CARCINOGENESIS (MEETING ABSTRACT).

Dao TL
Roswell Park Memorial Institute, Buffalo, NY
International Symposium on Health Effects of Tumor Promotion, October 12-15, 1981, Cincinnati, Ohio US Environmental Protection Agency and the American College of Toxicology; 1981

Both epidemiologic findings and experimental data provide convincing evidence to support the concept that the etiology of cancer is multifactorial. In experimental mammary carcinogenesis, polypeptide and steroid hormones have been shown to be involved in the initiation and promotion phases of mammary tumor induction. Among the environmental factors suspected to play a role in mammary carcinogenesis, dietary fat correlates well with breast cancer incidence. This paper will present experimental data to demonstrate the co-carcinogenic effect of hormones in the induction of mammary cancer in the rat by polycyclic aromatic hydrocarbons. The experimental data will be compared with human epidemiologic findings. The relationship between dietary fat and mammary carcinogenesis in experimental models will be presented and, finally, the possible relationship between dietary fat and hormones will be discussed. (no Refs)

104. GENETIC AND SEXUAL FACTORS IN CANCER (MEETING ABSTRACT).

Petrakis NL
No affiliation given
The Causes of Cancer, November 6, 1981, Los Angeles, California California Hospital Medical Center; 1981

Human cancers comprise a heterogeneous group of diseases with a diversity of causes. Genetic factors have been demonstrated to be associated with a number of human cancers. The discussion will include current knowledge of genetic factors in the major cancer sites, eg breast, colon-rectum, stomach, lung and skin. In addition, a brief presentation will be made on the major endocrine-dependent human cancers. (no Refs)

105. ESTROGEN- AND ANDROGEN/ESTROGEN-INDUCED AND -DEPENDENT TUMORS IN THE SYRIAN HAMSTER (MEETING ABSTRACT).

Kirkman H
Department of Structural Biology, Division of Human Anatomy, Stanford University School of Medicine, Stanford, CA, 94305

Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

The history of, and unanswered questions pertaining to, the following hamster tumors are discussed: estrogen-induced pituitary adenomas and renal carcinomas, androgen/estrogen-induced leiomyosarcomas of the ductus deferens and uterine horn, and similarly induced tumors of the scent gland; the estrogen-induced cystadenomas and carcinomas of the epididymal head, the carcinosarcomas and stromal nodules of the uterine horn, and the possible androgen/estrogen-induced stromal sarcomas of the uterine horn. Discussed also are: the relation of sex hormones to hepatic and mammary gland neoplasia, to fibroangioma and chondroma formation in the external ears, and to adrenal cortical and urinary bladder neoplasia. (no Refs)

106. STEROID HORMONES AND BREAST CANCER.

Adams JB
University of New South Wales, New South Wales, Australia

Diss Abstr Int [B]; 42(4):1425-B 1981

The thesis contains 49 papers. Early studies were undertaken on the biosynthesis of sulphated mucopolysaccharides (sulphated glycosaminoglycans) in embryonic chick cartilage. Studies were also undertaken on the chemical composition of the ground substance of the stroma of human mammary carcinoma tissue and on the mucin of colloid carcinoma of the breast. It was during these latter investigations that the linkage of carbohydrate prosthetic groups, via N-acetylhexosamine to serine and threonine residues, in this and other glycoproteins (including blood group substances) was established. Steroid sulphotransferases were discovered in human adrenal glands and also in human mammary carcinoma tissue and work proceeded on two fronts: firstly, the isolation and properties of steroid sulphotransferases, and secondly, on the biological significance of these enzymes in mammary tumors and other tissues. Intensive investigations were then made on steroid metabolism in human mammary carcinoma tissue and its intrinsic paraendocrine properties were revealed. The above data has been synthesized into a working hypothesis on hormones and breast cancer and the proposal made that C19 steroids unsaturated at position 5 (5-androstene derivatives) of the adrenal gland may be involved in an etiology of the disease. This hypothesis is currently being tested. (no Refs)

107. CURRENT STATUS OF PROGESTIN RECEPTORS IN CANCER (MEETING ABSTRACT).

Wittliff JL
Department of Biochemistry, University of Louisville Health Sciences Center, Louisville, KY

Clin Chem; 27(6):986 1981

Because the native hormone, progesterone, associates and dissociates rapidly from its binding sites in vitro, several synthetic steroids of high specific radioactivity are used as ligands in clinical assays. The most commonly employed is tritium-labeled R5020, a progestomimetic steroid, which has a high affinity for and dissociates slowly from receptors. Although the subunit structures of progestin receptors in chick oviduct are reasonably well understood, those of breast and uterus are emerging. Currently it is accepted that estrogens, via their own receptor mechanism, are involved in the control of progestin receptors in uterus. Although less is known of this regulatory mechanism in mammary tissues, it appears that analyses of progestin receptors in breast carinomas are helpful in the selection of hormonal manipulation. Patients with breast biopsies containing both estrogen and progestin receptors show an increased like lihood of responding to ablative or additive hormone therapy compared to those with only one type of receptor. Several new clinical trials by national cooperative groups are investigating the relationship between tumor receptor status and a patient's response to antihormone therapy and disease-free survival. These studies require quality assurance steroid receptors analyses and the establishment of uniformity of methods and data expression. (no Refs)

108. SYSTEMIC CATEGORIES FOR VERBAL AND OBSERVATIONAL EXAMINATION AND THEIR SIGNIFICANCE: BREASTS.

Kobayashi T
Dept. Obstetrics, Affiliated Hosp., Tokyo Univ. Sch. Medicine, Tokyo, Japan

Kango Gijutsu; 27(10):52-56 1981

Physiological changes during the development of breasts, significance of breast observations during nonpregnancy, and management and observations of breasts during pregnancy are discussed. Breast or mammary gland abnormalities included polymastia, polythelia, ectopic mammary glands, breast nodules, chronic mammary gland disease. fibromas, breast cancer, and prolactin abnormalities. Accessory mammae that are associated with polymastia are removed at infancy as malignant tumors occasionally develope from them. Ectopic mammary glands in the sternal or clavicular region should be removed as they are often the site of cancer development. Breast nodules can represent anything from adenomas to malignant breast cancer. Early stage cancer occurs in approx 9% or the cases of chronic mammary gland disease. Of breast tumor types, breast cancer occurs the most often (50-90%), and it occurs slightly more often on the left side; the most important early indication is a nodule that is rarely pressure-sensitive. One cause of prolactin abnormalities is pituitary adenoma. (no Refs) (In JPN)

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Calabrese EJ

Environmental Health Program, Div. Public Health, Univ. Massachusetts, Amherst, MA

Nutrition and Environmental Health: The Influence of Nutritional Status on Pollutant Toxicity and Carcinogenicity. Volume 2: Minerals and Macronutrients. New York, John Wiley and Sons, 468 pp., 1981.

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

2. RETROSPECT AND PROSPECT OF STUDIES ON DIGESTIVE SYSTEM DISEASES IN CHINA.

Zhang X

Dept. Internal Medicine, Capital Hosp., Chinese Acad. Medical Sciences, Beijing, People's Republic of China

Zhonghua Xiaohua Zazhi; 1(1):1-4 1981

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3. EPIDEMIOLOGY OF PITUITARY ADENOMAS.

Gold EB

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkins Univ., 615 Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:163-183 1981

4. BLADDER CANCER EPIDEMIOLOGY.

Matanoski GM, Elliott EA

Dept. Epidemiology, Sch. Hygiene and Public Health, Johns Hopkias Univ., 615 North Wolfe St., Baltimore, MD, 21205

Epidemiol Rev; 3:203-229 1981

5. THE EPIDEMIOLOGY OF BENIGN BREAST DISEASE.

Ernster VL

Dept. Epidemiology and International Health, 1699HSW, Univ. California, San Francisco, CA, 94143

Epidemiol Rev; 3:184-202 1981

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6. AIR POLLUTION AND BIOLOGICAL DEFENCE.

Schlipkoter HW, Dolgner R

Med. Institut fur Umwelthygiene an der Univ., Gurlittstrasse 53, D-4000 Dusseldorf 1, W. Germany

Zentralbl Bakteriol [Orig A]; 172(4/5):299-311 1981

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7. CANCER AND THE PHYSICOCHEMICAL QUALITY OF DRINKING WATER IN QUEBEC.

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Dept. Geography, Univ. Montreal, Montreal, Quebec, Canada

Soc Sci Med [Med Geogr]; 15(1):213-223 1981

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8. ONCOGENIC VIRUSES.

Wyke JA

Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England

J Pathol; 135(1):39-85 1981

9. ROLE OF VIRUSES IN THE ETIOLOGY OF NATURALLY OCCURRING FELINE LEUKEMIA.

Essex M, Grant CK, Cotter SM, Hardy Jr WD

Dept. Microbiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115

Haematol Blood Transfus; 26:483-487 1981

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10. MAMMALIAN IN VIVO AND IN VITRO CYTOGENETIC ASAYS: A REPORT OF THE U.S. EPA'S GENE-TOX PROGRAM.

Preston RJ, Au W, Bender MA, Brewen JG, Carrano AV, Heddle JA, McFee AF, Wolff S, Wassom JS

Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830

Mutat Res; 87(2):143-188 1981

11. BACTERIAL SYSTEMS FOR CARCINOGENICITY TESTING.

Mohn GR

Dept. Radiation Genetics and Chemical Mutagenesis, State Univ. Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

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Doll R

Radcliffe Infirmary, Oxford, England

S Afr Cancer Bull; 25(3):125-146 1981

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health • National Cancer Institute

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PREVALENCE OF BREAST CANCER IN HUMAN POPULATIONS

1. BREAST CANCER IN DENMARK DURING THE PERIOD 1943-1976. CANCER STATISTICS 3.

Ewertz M
Cancerregisteret, Copenhagen, Denmark
Ugeskr Laeger; 143(42):2758-2760 1981

Statistical data are presented on breast cancer in Denmark during the period 1943-1976. The number of cases diagnosed per yr has increased from 1,038 in 1943-1947 to 2,173 in 1973-1976 in women and from 9 to 19 in men during the corresponding periods. In women, the breast cancer incidence (per 100,000 women) has increased from 59.3 in 1943-1947 to 80.6 in 1973-1976, while the mortality rate was 33.1 in 1943-1947 and 37.4 in 1973-1976. The incidence of breast cancer in women av 71.8 in Copenhagen, 63 in provincial towns, and 48.4 in rural areas in 1943-1947, and 89.8 in Copenhagen, 82.8 in provincial towns, and 71.9 in rural areas in 1973-1976, ie, there has been a tendency to equalization. The increase in incidence has affected all age groups. There has been a slight increase in survival rate, which was most pronounced for the cases diagnosed between 1943 and 1957. (9 Refs) (In DAN)

2. CANCER MORBIDITY IN THE USSR IN 1978.

Napalkov NP, Merabishvili VM, Tserkovnyi GF, Preobrazhenskaia MN
No affiliation given
Vopr Onkol; 27(9):3-23 1981

The incidence of various malignant tumors in the population of the Soviet Union in 1978 is reviewed. In 1978 there was a 1.2% increase in rate of overall cancer morbidity, compared with the rates for 1976 and 1977. Breast cancer moved from third place to second place in female cancer morbidity. Incidences of pharyngeal, mouth, rectal, skin, breast, lymphatic, and hematopoietic neoplasms increased in the urban population, while incidences of these cancers in the rural population decreased or remained stable. Stomach, lung, and skin neoplasms had the highest incidences; this was true in both the urban and the rural populations. The next most frequent neoplasms in the urban population were breast, lymphatic, and hematopoietic, whereas the next most frequent in the rural population were cervix, esophageal, and lip. (9 Refs) (In RUS)

3. HISTOLOGICAL AND EPIDEMIOLOGICAL FEATURES OF BREAST CANCER IN DIFFERENT RELIGIOUS GROUPS IN GREATER BOMBAY.

Jussawalla DJ, Yeole BB, Natekar MV
Indian Cancer Society, Parel, Bombay 400 012, India
J Surg Oncol; 18(3):269-279 1981

In this paper an attempt has been made to study the histologic and epidemiologic features of breast cancer in women from various religious groups of Greater Bombay. The crude and age-adjusted incidence rates are seen to be the highest in the Parsi community followed by the Christian, Moslem, and Hindu groups. In all the religious groups, an increase in incidence of breast cancer is first seen in the third decade. This is followed by a sharp increase up to the age of 50-54, leading to a slight drop, and then a consistent but slower rise in the older ages. The high risk of developing this cancer in Parsi women as comared with the Christian, Moslem, and Hindu experience may be due to a higher proportion of Parsi women remaining unmarried, their higher age at marriage, lower age at first pregnancy, broad spacing of pre gnancies, and fewer numbers of pregnancies. The distribution according to histologic types of breast cancer in India is characterized by a high frequency of infiltrating duct carcinoma. Medullary, lobular, and squamous cell carcinoma were typical histological varieties of the older age groups, whereas ductal carcinoma was encountered mostly in premenopausal women. (Author abstract) (18 Refs)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

4. A PROSPECTIVE STUDY OF PLASMA PROLACTIN LEVELS AND SUBSEQUENT RISK OF BREAST CANCER.

Kwa HG, Cleton F, Wang DY, Bulbrook RD, Bulstrode JC, Hayward JL, Millis RR, Cuzick J

Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., Plesmanlaan 121, 10066CX Amsterdam, The Netherlands

Int J Cancer; 28(6):673-676 1981

Plasma prolactin was measured in 2,572 premenopausal, 628 menopausal, and 1,666 peri- and postmenopausal women who were apparently healthy. Breast cancer was subsequently diagnosed in 47 of these women at a median time of 5 years after blood collection (pre-cancer cases). Prolactin levels in premenopausal cases increased significantly with age whereas this was not found in matched controls. The perimenopausal cases were characterized by extreme variability in prolactin levels. In post-menopausal women who developed breast cancer, the prolactin levels were significantly elevated, being at or above the 70th percentile for the controls. In this group the results are consistent with prolactin acting as a late-stage tumor promoter. (Author abstract) (18 Refs)

5. TUMOUR SPECTRUM IN THE FAMMM SYNDROME.

Lynch HT, Fusaro RM, Pester J, Oosterhuis JA, Went LN, Rumke P, Neering H, Lynch JF

Dept. Preventive Medicine/Public Health, Creighton Univ. Sch. Medicine, Omaha, NE, 68105

Br J Cancer; 44(4):553-560 1981

The familial atypical multiple mole-melanoma syndrome (FAMMM) is characterized by an autosomal dominantly inherited susceptibility to multiple atypical nevi. patients with this hereditary phenotype show a strong susceptibility to cutaneous malignant melanoma (CMM). Our investigation of an extended Dutch kindred showing the FAMMM phenotype revealed a proband with bilateral intraocular malignant melanoma (IOM) and multiple CMM. The family revealed an array of tumors which included carcinoma of the lung, skin, larynx, and breast in addition to CMM and IOM, which were transmitted vertically through three generations. There was male-to-male transmission, and the number of affected males and females was about the same, which was consistent with an autosomal dominant inheritance. Thus the FAMMM syndrome not only indicates a potential for CMM, but a susceptibility to other systemic cancers as well. These observations, though limited to a single kindred, merit a painstaking evaluation of cancer of all anatomical sites in other kindre ds showing the FAMMM syndrome. Such studies could yield clues to cancer etiology, pathogenesis, and control. (Author abstract) (22 Refs)

6. BILATERAL MAMMARY CARCINOMAS AS RISK FACTORS: OUR EXPERIENCE.

Ricci G, Forin M, Berlanda G, Lise M, Di Maggio C, Pescarini L
Istituto di Clinica Chirurgica, Universita di Padova, Padova, Italy
Radiol Med (Torino); 67(11):892-893 1981

Five hundred and sixty four cases of mammary carcinoma (MC) are discussed. Of the 564 MC, 37 were bilateral (6.5%) including 25 asynchronous (ie underwent mastectomy 6 mo later), 12 synchronous, and 2 asynchronous, but with mastectomy within 6 mo. The 5 yr survival rate for synchronous cases was 80.8% and 40.4% for 10 yr. The incidence of developing MC in the second breast was higher than reported in literature. Mastectomized patients are at higher risk of developing MC in the remaining breast, especially if they are young. No increase in mortality was noticed in patients who underwent bilateral MC. (6 Refs) (In ITA)

7. DIETARY FACTORS AND BREAST CANCER RISK.

Lubin JH, Burns PE, Blot WJ, Ziegler RG, Lees AW, Fraumeni JF
Environmental Epidemiology Branch, NCI, Bethesda, MD
Int J Cancer; 28(6):685-689 1981

As part of a case-control study in northern Alberta, Canada, 577 women aged 30-80 with breast cancer diagnosed during 1976-77 and a population-based age-stratified random sample of 826 disease-free female controls were questioned about certain aspects of their diet. Computing relative risks (RRs) by tertiles, significant increasing trends were found with more frequent consumption of beef (RRs of 1.0, 2.3, 1.5; test for trend, p less than 0.001), pork (RRs of 1.0, 1.6, 2.2; test for trend, p less than 0.001), and sweet desserts (RRs of 1.0, 1.3, 1.5; test for trend, p = 0.01). Elevated risks were also noted for use of butter at the table and for frying with butter or margarine, as opposed to vegetable oils. The association of total beef and pork consumption with breast cancer was not materially affected by controlling for age at first birth, family history of breast cancer, previous benign breast biopsy or socioeconomic status. Nor was the association reduced by controlling for ages of menarche and menopause, even though within the control series the intake of beef and pork reported in adult life was higher among those with a lower age at menarche or an older age at natural menopause. (Author abstract) (26 Refs)

8. CYTOLOGICAL ABNORMALITIES IN NIPPLE ASPIRATES OF BREAST FLUID FROM WOMEN WITH SEVERE CONSTIPATION.

Petrakis NL, King EB
Dept. Epidemiology and International Health, Univ. California, San Francisco, CA, 94143
Lancet; 2(8257):1203-1205 1981

The relation between epithelial dysplasia in nipple aspirates of breast fluid and frequency of bowel movements was studied in 1,481 white women. There was a significant positive association with dysplasia (risk ratio 4.5; 95% confidence interval 1.9-11.9) in women reporting severe constipation, ie, two or fewer bowel movements weekly, which was not seen in women reporting more than one bowel movement daily. Women who had one bowel movement daily or one every other day had increased risk ratios. Cytological abnormalities in breast epithelium associated with severe constipation may be relevant to studies of diet and breast disease since the intestinal flora has been reported to metabolize bile salts and estrogens secreted by the liver into the gastrointestinal tract - a process which may be enhanced by severe constipation. (Author abstract) (36 Refs)

9. A COHORT STUDY ON CANCER AMONG WORKERS EXPOSED TO AN ANTIRUST OIL.

Jarvholm B, Lavenius B
Dept. Occupational Medicine, Sahlgrenska Sjukhuset, S-413 45 Goteborg, Sweden
Scand J Work Environ Health; 7(3):179-184 1981

An epidemiologic study of workers in an engineering company was conducted following the observation of three cases of cancer among women who wrapped bearing rings covered with antirust oil. Group A (98 persons) worked in the same packing department as the three affected women between 1954 and 1957 and were exposed to white spirit, mineral oil, lanolin, zinc naphthenate, and N-phenyl-1-naphthylamine + sodium nitrite. Group B (33) worked in another packing department and were exposed to mineral oil, vaseline, and stearic acid + sodium nitrite. Group C (31) had been treated for eczema from antirust oil in 1955 and had been exposed to white spirit, mineral oil, lanolin, zinc naphthenate, and N-phenyl-1-naphthylamine. Twelve cancers were found only among the women in Group A (expected value was 3.9 cancers); four cancers each were found in Group B and C (expected values were 2 and 3.8, respectively). The cancers in Group A were in the colon, breast, collum of the uterus (4), ovary (2), bladder, brain, thyroid, and reticulosarcoma. Two workers in Group C developed cancer of the bladder, one of whom was also included in Group A. The most likely etiological agent for Group A cancers is N-phenyl-1-naphthylamine, either alone or in combination with sodium nitrite. (15 Refs)

10. PRIMARY MULTIPLE BILATERAL BREAST CANCER.

Popova RT
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Vopr Onkol; 27(10):92-97 1981

Literature data on the etiology and management of primary multiple bilateral breast neoplasms (PMBBN) are reviewed. The incidence of PMBBN ranges from 0.8% to 19.6% (in different studies). Etiology of PMBBN is associated with neurohormonal disorders. Multicentric growth and bilateral involvement is related to the histological type of the tumor. The period between detection of the first and second tumors ranges from 3 mo to 3 yr for synchronous neoplasms and up to 29 yr for metachronous neoplasms. The risk of involvement of the second breast in the patients with unilateral breast cancer is 3-21x greater than that in the general population. The 5-yr survival rates for the patients with synchronous and metachronous PMBBN was 47.6% and 75.5%, respectively. (56 Refs) (In RUS)

11. EARLY AGE AT FIRST BIRTH AND DECREASED RISK OF BREAST CANCER.

Bain C, Willett W, Rosner B, Speizer FE, Belanger C, Hennekens CH (c/o Hennekens), Channing Lab., 180 Longwood Ave., Boston, MA, 02115
Am J Epidemiol; 114(5):705-709 1981

The relationship between age at birth of a first child and breast cancer was evaluated for 1,159 affected women and 11,590 women without cancer in data collected in 1976 among married female registered nurses residing in 11 states in the United States. A positive trend of increasing risk of breast cancer with later ages at first birth was found (chi21 for trend in proportions = 30.9, p less than 0.01). Adjustment for potential confounding variables by multiple logistic regression did not affect this trend. The presence of this relationship using non-hospitalized controls of similar social status to cases supports the reality of this association, which has recently been challenged as an artifact due to inappropriate choice of hospitalized controls. (Author abstract) (22 Refs)

12. SERUM PROLACTIN, ANDROGENS, OESTRADIOL AND PROGESTERONE IN ADOLESCENT GIRLS WITH OR WITHOUT A FAMILY HISTORY OF BREAST CANCER.

Boffard K, Clark GM, Irvine JB, Knyba RE, Bulbrook RD, Wang DY, Kwa HG
(c/o Wang) Dept. Clinical Endocrinology, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London, England
Eur J Cancer Clin Oncol; 17(10):1071-1077 1981

Serum levels of prolactin, progesterone, estradiol, androstenedione and dehydroepiandrosterone sulfate have been measured in 52 adolescent girls with a family history of breast cancer and 90 girls without such a history. Using conventional statistical tests no significant differences were found in the endocrine status of the two groups. (Author abstract) (26 Refs)

13. UNOPPOSED ENDOGENOUS ESTROGENS AND THE INCIDENCE OF CANCER IN FEMALE REPRODUCTIVE ORGANS.

Johansson ED, Messinis JE, Nillius SJ
Dept. Obstetrics and Gynecology, Univ. Hosp., S--750 14 Uppsala 14, Sweden
Acta Obstet Gynecol Scand [Suppl]; (101):17-20 1981

Changes in the reproductive behavior (early menarche and late menopause, decline in number of pregnancies and live births, increases in sterile menstrual cycles) of women in industrialized nations and epidemiological studies linking the changes to breast, ovarian, and endometrial cancer are reviewed. The studies implicate unopposed endogenous estrogen production in the increased incidence of cancer of the reproductive organs and support the concept that use of progestins could halt this trend. (29 Refs)

14. SOME ASPECTS OF THE ENDOCRINE STATUS IN THE INFLAMMATORY BREAST CARCINOMA (MASTITIS CARCINOSA).

Kiricuta I, Frenkel Z
(c/o Frenkel), Inst. Oncology, Str. Republicii 34-36, 3400 Cluj-Napoca, Romania
Arch Geschwulstforsch; 52(1):67-73 1982

Endocrine parameters in 87 patients with inflammatory breast carcinoma (IBC) of rapid evolution (Group I) were compared with those in 400 patients with noninflammatory breast carcinoma (NBC) of normal evolution (Group II). Total urinary estrogens were measured in 81 patients from Group I and in 326 patients from Group II. Urinary 17-ketosteroids were measured in 60 patients from Group I and 61 patients from Group II. Mean age at menarche was significantly higher (14.8 +-0.22 yr) in Group I than in Group II (14.0 +-0.06 yr). Menarche at 16 yr or later occurred in 36.8% of Group I compared with 16.75% of Group II. Mean number of abortions was lower in Group I (1.72) than in Group II (2.16). Cases with no abortions were more frequent (48.1%) in Group I than in Group II (41.7%). Mean levels of urinary ethiocholanolone (Et) were low in Group I (0.66 +-0.04 mg/24 hr) than in Group II (1.04 +-0.08 mg/24 hr). The androsterone/Et ratio was higher (1.00) and the Et/11-oxygenated-17-ketosteroids ratio was lower (0.72) in group I than in group II (0.75 and 0.91, respectively). Results indicate a greater hormonal imbalance in IBC than in NBC. (49 Refs)

15. SURVEILLANCE AND MANAGEMENT OF HEREDITARY BREAST CANCER.

Lynch HT, Albano WA, Organ CH, Schmitz GD, Lynch JF
Dept. Preventive Medicine/Public Health, Creighton Univ. Sch. Medicine, Omaha, NE
Breast; 7(4):2-9 1981

Clinical and biological characteristics of hereditary breast cancer are discussed to aid in establishing guidelines for its effective surveillance and management. Characteristics include significant early age of onset, excess of bilaterality and/or specific tumor associations, vertical transmission, and improved survival over nonhereditary forms. Recent observations suggest that a genetic linkage exists between breast cancer susceptibility and the glutamate-pyruvate transaminase locus in breast cancer prone families. Consistently lower plasma levels of prolactin, gonadotropin, estrone, and estradiol were measured in a high risk population, although the differences were not statistically significant. Oral contraceptives may act synergistically with other risk factors such as nutritional changes, alcohol usage, and increased cigarette smoking and may be primarily operative in familial breast cancer. Surveillance techniques include family counseling, monthly breast self-examination, biannual physician breast examination, mammography every 2 yr, and immediate biopsy of all dominant nodules. Existing breast cancers should receive standard evaluation and treatment, and the contralateral breast should be evaluated by mammogram and biopsy. The control of hereditary breast cancer could be aided immeasurably by the assembly of breast cancer prone kindreds in a carefully designed study. (35 Refs)

16. TWO FAMILIES WITH CANCER FAMILY SYNDROME.

Bulow S, Svendson LB, Shannon Danes B
Kirurgisk-gastroenterologisk afdeling, Bispebjerg hospital, Copenhagen, Denmark
Ugeskr Laeger; 143(42):2716-2718 1981

Cancer family syndrome (CFS) in two families is reported. One family had 30 members in 4 generations, and reliable information is available on 29 members. Cancer was found in 11/29 cases (4 men and 7 women, age at the manifestation of the first cancer 33-38 yr, av 56 yr). The tumors included four colorectal carcinomas, four solitary colorectal adenomas, one skin cancer, two breast cancers, one gastric cancer, and one cancer of uterine cervix. Two primary cancers were found in one patient. Increased tetraploidy of skin fibroblasts, investigated in 13/29 cases, was found in 6/13 family members, 2 of whom were affected by cancer. The other family included 25 members in 4 generations; reliable information is available for 23 family members. Six members of this family, including three men and three women, had cancer: nine colorectal cancers and one retroperitoneal malignant tumor were diagnosed. There were 10 primary malignant tumors. The age of the patients at the time of manifestation of the first tumor was 37-51 yr (av 41 yr). Increased tetraploidy of kin fibroblasts, investigated in 10 family members, was found in 5/10 cases, including in 2 cancer patients. (8 Refs) (In DAN)

17. CANCERS OF THE BREAST AND FEMALE GENITAL SYSTEM: SEARCH FOR RECESSIVE GENETIC FACTORS THROUGH ANALYSIS OF HUMAN ISOLATE.

Simpson JL, Martin AO, Elias S, Sarto GE, Dunn JK
Section Human Genetics, Dept. Obstetrics and Gynecology, Prentice Women's Hosp. and Maternity Center, 333 East Superior St., Chicago, IL, 60611
Am J Obstet Gynecol; 141(6):629-636 1981

To investigate the importance of recessive genes in female breast and genital cancers, we have conducted investigations in the Hutterites, a highly inbred genetic isolate in North America. The homogeneous life style of this group, which lives on communal farms, also facilitates distinction between shared environmental and genetic factors. We ascertained 177 cases of cancer (all organ systems) through Canadian and United States cancer registries, field trips, and searches of death certificates. Breast cancer and endometrial cancer mortalities were those expected for 1970 United States whites, but no deaths due to squamous cervical carcinoma were ascertained in this monogamous population. Inbreeding coefficients (F) for cases were higher than means for matched controls for each of the four cases of breast cancers that occurred in younger women (less than 45 yr of age), for four of five cases of endometrial cancer, and for the single cases of uterine leiomyosarcoma, dysgerminoma, and ovarian adenocarcinoma. By contrast, in cases of breast cancer that occurred in women 45 yr of age or older, only four of 15 F's were above those for controls. There is a significant difference between the two breast cancer age groups with respect to the likelihood that the F of cases was higher than the F of controls (X2 = 6.99, p less than 0.01). However, grouping cases by type, none of the F distributions were significantly different from those of their matched controls. These preliminary genetic investigations thus confirm certain concepts concerning breast and female genital cancer but also suggest the desirability of further studies to elucidate the role of genetic factors in premenopausal breast cancer. (Author abstract) (16 Refs)

18. RISK FACTORS FOR BREAST CANCER: A TABULAR SUMMARY OF THE EPIDEMIOLOGICAL LITERATURE.

Kalache A
Dept. Community Medicine, Univ. Oxford, 8 Keble Road, Oxford OX1 3QN, England
Br J Surg; 68(11):797-799 1981

Nine categories of postulated risk factors for breast cancer and the approx relative risk for each factor are tabulated with key references. The categories are demographic, anthropometric, dietary, hormonal exposure, other exposure (ionizing radiation, drugs that increase prolactin secretion), and menstrual, reproductive, family, and past medical history. (38 Refs)

POSSIBLE IATROGENIC FACTORS IN HUMAN BREAST CARCINOGENESIS

19. EXOGENOUS ESTROGENS AND BREAST CANCER.

Lawson DH, Jick H, Hunter JR, Madsen S
(c/o Jick), Boston Collaborative Drug Surveillance Program, 400 Totten Pond Road, Waltham, MA, 02154
Am J Epidemiol; 114(5):710-713 1981

Rates of breast cancer at Group Health Cooperative of Puget Sound, Seattle, Washington, a health maintenance organization, remained stable from 1972-1979 in women aged 30-44 yr and in women aged 55-64 yr, despite the fact that the frequency of use of estrogen-containing drugs has varied substantially. By contrast, rates of breast cancer in women aged 45-54 yr appear to have fallen since 1977 in association with a substantial fall in estrogen use in women of this age group. The results are consistent with an etiologic role for current exogenous estrogen in breast cancer in middle-aged women. (Author abstract) (7 Refs)

20. ORAL CONTRACEPTION AND CANCER RISK.

Genton CY
Leitender Arzt, Abteilung fur Gynakopathologie, Institut fur Pathologie der Universitat, Universitatsspital, CH-8091 Zurich, Switzerland
Schweiz Med Wochenschr; 111(46):1742-1748 1981

Oral contraception was introduced 20 yr ago and is today the most popular method of preventing pregnancy. Some undesirable side effects of these drugs are well known, while others are only suspected. Many investigations have been undertaken to elucidate whether or not the Pill has carcinogenic properties, and the present study describes the current state of knowledge on this question. At present no evidence exists to suggest that oral contraceptives have carcinogenic effects on the human breast or genital organs. A causal relationship between use of these drugs and development of liver tumors is possible but far from proven. (Author abstract) (39 Refs) (In GER)

21. RADIATION-INDUCED MAMMARY CARCINOGENESIS IN VIRGIN, PREGNANT, LACTATING, AND POSTLACTATING RATS.

Holtzman S, Stone JP, Shellabarger CJ
Medical Dept., Brookhaven Natl. Lab., Upton, NY, 11973
Cancer Res; 42(1):50-53 1982

Little attention has been paid to the influence of reproductive condition of the rat at the time of irradiation upon x-ray-induced mammary carcinogenesis. At 12 wk of age, 160 virgin female Sprague-Dawley rats were mated, and another 140 were maintained as virgins. On Days 14 to 16 of pregnancy, 36 mated females and 40 virgins were whole-body irradiated with 200 R of x-rays. On Days 2 to 5 postpartum, 40 additional mated females and 40 additional virgins were irradiated. At this time, all pups were removed from their mothers; 2 wk later, 40 additional parous females and 40 virgins were irradiated. The remaining animals: parous females; virgins; and mated, but nonparous females were kept as unirradiated controls. Brest tissue biopsies were taken from 25% of the animals in each irradiated group on the day of irradiation, and the biopsies were examined microscopically for mammary tissue development. The experiment was terminated 10 mo after irradiation. Despite marked differences in mammary tissue development among the groups at the time of irradiation, there were no significant differences among the irradiated groups for the incidence of rats with mammary adenocarcinomas or the number of mammary adenocarcinomas per rat. There were no significant differences among the irradiated groups for the incidence of rats with mammary fibroadenomas. There was an increase in the number of fibroadenomas per rat which was associated with increased age at the time of death. In contrast to mammary carcinogenesis produced by polycyclic aromatic hydrocarbons in previous studies, in the current investigation the physiological status of the host at the time of irradiation had little effect on: (a) the final incidence of mammary neoplasia; (b) the number of mammary adenocarcinomas produced; or (c) the type of mammary neoplasms produced. (Author abstract) (29 Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

22. INFLUENCE OF AGE AND PARITY ON THE SUSCEPTIBILITY OF RAT MAMMARY GLAND EPITHELIAL CELLS IN PRIMARY CULTURES TO 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Russo J, Wilgus G, Tait L, Russo IH
Experimental Pathology Lab., Dept. Biology, Michigan Cancer Foundation, 110 E. Warren Ave., Detroit, MI, 48201
In Vitro; 17(10):877-884 1981

Mammary gland epithelial cells from rats of different ages or with different reproductive histories vary in their proliferative properties and susceptibility to dimethylbenz(a)anthracene (DMBA) carcinogenesis in vivo. The present study was carried out to determine whether these differences are maintained under in vitro conditions. Primary cultures of mammary gland epithelial cells of young virgin, old virgin, and parous rats were treated with various doses of DMBA. Growth rates, DNA synthesis, and dose-response curves were determined; the toxicity of DMBA was measured by its effect on cell growth. Cell morphology was studied by transmission and scanning electron microscopy. Epithelial cells from the mammary gland of young virgin rats adapted rapidly to the culture conditions, behaving as if the cells were in the logarithmic phase of growth prior to plating. Mammary gland epithelial cells from old virgin and parous rats required a lag period prior to cell growth during which the proliferating cells adapted to the culture conditions. Cells from each group had comparable doubling times, and DNA synthesis peaked approx 1 day after initiation of growth in culture. The numbers of proliferating cells decreased with increasing age and parity of the donor. Mammary gland epithelial cells of young virgin rats were more susceptible to both low and high doses of DMBA than those of old virgin and parous rats when the carcinogen was added either 24 hr after plating or at the peak of DNA synthesis. These results indicate that age and parity influence the proliferative status of the cells and their susceptibility to DMBA in vitro, simulating in that way the in vivo situation. (Author abstract) (35 Refs)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

23. THE EFFECT OF DISULFIRAM ON THE CARCINOGENICITY OF 3,2'-DIMETHYL-4-AMINOBIPHENYL IN SYRIAN GOLDEN HAMSTERS AND RATS.

Fiala ES, Weisburger JH, Katayama S, Chandrasekaran V, Williams GM
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Carcinogenesis; 2(10):965-969 1981

Species differences in 3,2'-dimethyl-4-aminobiphenyl (DMAB) carcinogenicity, which induces mostly bladder tumors in Syrian hamsters and intestinal and breast tumors in rats, were investigated. Groups of male Syrian golden hamsters received sc injections of DMAB weekly for up to 22 mo (total av cumulative dose 555 mg) either alone or simultaneously with disulfiram in the diet. At the tolerated dose of disulfiram (2.5 mg/kg), the overall tumor yield induced by DMAB alone was not affected, but the number of small intestine tumors was reduced and the appearance of bladder and colon cancers was delayed. In two groups of male Charles River rats, weekly sc injection of DMAB (20 mg/kg) for 37 wk (total av cumulative dose 289 or 241 mg) induced primarily intestinal cancers. As in hamsters, addition of disulfiram to the diet of the second group reduced the incidence of small intestine cancers but resulted in the appearance of a small number of bladder cancers. DMAB-treated rats also developed in situ prostatic carcinoma, regardless of whether they were treated with or without disulfiram. (19 Refs)

24. INFLUENCE OF PROLACTIN AND GROWTH HORMONE ON RAT MAMMARY TUMORS INDUCED BY N-NITROSOMETHYLUREA.

Rose DP, Noonan JJ
Div. Clinical Oncology, Wisconsin Clinical Cancer Center, Univ. Wisconsin, Madison, WI, 53792
Cancer Res; 42(1):35-38 1982

The effects of hypophysectomy and prolactin-suppressing drugs on the growth of mammary tumors induced in Sprague-Dawley rats by N-nitrosomethylurea and dimethylbenz(a)anthracene were compared. The influence of ovine prolactin and growth hormone administration on N-nitrosomethylurea-induced tumors was also studied in hypophysectomized animals. After hypophysectomy, all 13 tumors induced in 13 rats by N-nitrosomethylurea underwent regression, as did 10 of 12 induced by dimethylbenz(a)anthracene. There were no new tumors. Pergolide mesylate, a long-acting ergoline derivative, was given in a dose of 80 ug bid by sc injection for 28 days. Only 3 of 12 N-nitrosomethylurea-induced tumors regressed, while 4 became static. However, only two new tumors developed in the 12 pergolide-treated rats, compared to 11 in the 12 untreated controls. Bromocriptine mesylate, at 10x the pergolide dose, was even less effective; one of 16 tumors regressed, 2 became static, and 8 new tumors appeared in the 16 rats. In contrast, 8 of 12 dimethylbenz(a)anthracene-induced tumors regressed during pergolide therapy, 2 became static, and there was only 1 new tumor among the 12 rats. Prolactin, 1 mg bid for 7 days by sc injection, was given to another eight rats bearing 11 N-nitrosomethylurea-induced tumors, commencing 7 days after hypophysectomy. Regression of five tumors borne by four rats was reversed but resumed when treatment was stopped. Regression of five tumors in the other four animals was arrested without regrowth; the sixth became impalpable. All of these six grew rapidly when growth hormone, 2 mg bid, was administered in addition to prolactin. (Author abstract) (21 Refs)

25. SERUM CHOLESTEROL AND 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY CARCINOGENESIS.

Klurfeld DM, Kritchevsky D
Wistar Inst. Anatomy and Biology, 36th St. at Spruce, Philadelphia, PA, 19104
Cancer Lett; 14(3):273-278 1981

Tumor formation induced by po administration of 5 mg of the mammary carcinogen dimethylbenz(a)anthracene in female Sprague-Dawley rats was studied as a function of serum cholesterol level. Changes in serum cholesterol were induced by subjecting animals to one of three diets: (a) semipurified chole sterol-free (SP), (2) the same diet with 1.5% cholesterol and 0.5% bile salts added (CB), and (3) diet CB until treatment with DMBA, followed by diet SP thereafter. No significant differences were discernible in body wt due to diet or carcinogen administration throughout the study. Tumor incidence was similar in all groups (69-73%). Total tumor yield was significantly greater in Group 2 than in the other groups. Tumor vol and wt were similar in the three groups. Latency period of tumor appearance was 2 wk longer in Group 1 than in other groups. Group 2 had at least 2x as many palpable tumors as Group 1, while Group 3 was intermediate in occurrence. (20 Refs)

26. COMPARISON OF THE EFFECT OF BUTYLATED HYDROXYTOLUENE ON N-NITROSOMETHYLUREA AND 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMORS.

King MM, McCay PB, Kosanke SD
Biomembrane Res. Lab., Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
Cancer Lett; 14(3):219-226 1981

The effects of butylated hydroxytoluene (BHT) on nitrosomethylurea (NMU)- and 7,12-dimethylbenz(a)anthracene (DMBA)-induced rat mammary tumors were examined. Female Sprague-Dawley rats were fed either control diets or diets plus 0.3% BHT, and further divided into NMU-treated, DMBA-treated, or nontreated groups. DMBA was administered at 10 mg in 1 ml stripped corn oil intragastrically at 50 days of age. NMU was administered at 5 mg/100 g body wt iv in the tail vein at 50 days of age. A 100% incidence of tumors was seen in rats treated with DMBA and on the control diet. The incidence was reduced to 54% by addition of BHT to the diet. No difference in tumor incidence was seen in NMU-treated animals with or without addition of BHT. The differences in tumor prophylaxis may reflect the fact that DMBA is metabolized by the monooxygenase system but NMU is not. (30 Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

27. EFFECT OF ESTROGEN AND PROGESTERONE ON CELLULAR REPLICATION OF HUMAN BREAST TUMORS.

Dao TL, Sinha DK, Nemoto T, Patel J
Dept. Breast Surgery, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Res; 42(1):359-362 1982

A total of 54 infiltrating carcinomas of the breast were studied for estrogen receptor concentration in the tumor cytosol and thymidine-labeling indexes. The results showed that there was no significant difference in the level of thymidine-labeling index between 22 primary and 32 metastatic breast cancers. No significant association between the levels of thymidine-labeling index and the presence or absence of estrogen receptors was observed. The effect of 'physiological' doses of estrogen and progesterone on cell proliferative activity was studied by the level of thymidine-labeling indexes in the tumor cells in 10 patients with multiple skin and sc metastases. Tumor biopsies were performed for labeling indexes both before and after hormonal treatment. The results showed that physiological doses of estrogen and progesterone induced a significant rise in thymidine-labeling index within 3 days after hormonal treatment in 7 of the 10 tumors. Of the seven tumors that showed a rise in thymidine-labeling index, three were estrogen receptor positive and four were estrogen receptor negative. Of the three nonresponsive tumors, one was estrogen receptor positive and two were estrogen receptor negative. The study suggests that estrogen and progesterone can induce cell replication in both estrogen receptor-positive and -negative tumors. (Author abstract) (18 Refs)

28. ESTROGEN INDUCED GROWTH OF HUMAN BREAST CANCER CELLS (MCF-7) IN ATHYMIC NUDE MICE IS ENHANCED BY SECRETIONS FROM A TRANSPLANTABLE PITUITARY TUMOR.

Welsch CW, Swim EL, McManus MJ, White AC, McGrath CM
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
Cancer Lett; 14(3):309-316 1981

The influence of pituitary hormones on growth of MCF-7 human breast tumor cells maintained in athymic nude mice was investigated. Sc injection of a pellet containing 17B-estradiol, and estrone in drinking water (0.5 mg/liter), resulted in sustained growth of the cells. Injection of a prolactin/growth hormone secreting rat pituitary tumor into the estrogen treated mice also caused growth of the tumor cells. No growth of tumor cells was observed in animals injected with pituitary tumor alone or in animals receiving neither pituitary tumor nor estrogen. Thus, rat pituitary tumor secretions enhanced the rate of in vivo MCF-7 tumor growth in estrogen treated animals, suggesting a synergism in their respective actions. (16 Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

29. HISTOLOGICAL IDENTIFICATION OF CARCINOEMBRYONIC ANTIGEN IN BREAST CANCER. USE OF AN IMMUNOHISTOCHEMICAL TECHNIQUE IN 71 CASES OF BREAST CANCER.

Bonetti F, Maconi A, Pisa R, Menestrina F, Novelli P, Iannucci A, Chilosi M, Rasniewskij K
Istituto di anatomia, Universita di Padova, Verona, Italy
Pathologica; 73(1026):639-647 1981

A modification of the Burns technique using tagged antibodies and peroxidase was used in the determination of carcinoembryonic antigen (CEA). The CEA can be observed inside the cytoplasm as granules of variable size or as finely dispersed dust. This technique may also be used also in the retrospective study of prepared paraffin sections. Of the 71 infiltrating mammary carcinomas studied, 58 were positive and 13 negative. The CEA positive results were expressed as percent of CEA positive cells in relation to total number of neoplastic cells. The results varied according to histological type of mammary carcinoma (MC). Of 49 infiltrating ductal MC, 4 were negative, 8 showed 1-30%, 26 showed 30-70%, and 11 showed 70-100% positive cells. The results for 11 lobular infiltrating MC were 4, 5, 1, and 1, respectively. Of the 5 medullary MC, 2 were negative and 3 showed 70-100% positive cells. Of the 4 papillary MC, 2 were negative and 2 showed 30-70% positive cells. Of the 2 colloid MC, 1 was negative and 1 showed 1-30% positive cells. A larger sample is necessary to determine the significance of these results. (21 Refs) (In ITA)

30. SERIAL DETERMINATION OF CARCINOEMBRYONIC ANTIGEN IN THE FOLLOW-UP OF PATIENTS WITH MALIGNANT TUMORS.

Elmermacher H, Schuster P, Beyer HK
Innere Abteilung, St.-Marien-Spital, Bergstr. 56, 5800 Hagen 1, W. Germany
Minerva Med; 72(48):3259-3262 1981

Fifty four patients with carcinomas (27 mammary, 12 bronchial, 3 ovarian, 3 uterine, 2 malignant lymphomas, 2 thyroid, 2 urinary vesicle, and one each stomach, esophagus, and skin) underwent serial carcinoembryonic antigen (CEA) determination. The patients were divided into three groups. Group A, was composed of 21 patients in remission following cytostatic, hormonal or irradiation therapy (IT). Group B, consisted of 16 patients who showed no improvement after different IT. Group C consisted of 17 patients who received no IT. The patients were observed for 2-18 mo. CEA controls were performed 2-12x. A good correlation was found between tumor growth and CEA levels. This was especially true for Group A patients. (8 Refs) (In ITA)

31. ISOLATION AND ELECTROPHORETIC ANALYSIS OF IMMUNE COMPLEXES FROM PATIENTS WITH BREAST CANCER.

Gilead Z, Troy FA, Sulitzeanu D
Lautenberg Center General and Tumor Immunology, Hebrew Univ.-Hadassah Medical Sch., Jerusalem, Israel
Eur J Cancer Clin Oncol; 17(11):1165-1176 1981

Immune complexes (IC) were isolated from sera of patients with breast cancer (BC), from effusions from patients with breast and ovarian cancer (OC) and from effusions from patients with non-malignant diseases. Isolation was carried out with the aid of tubes coated with rheumatoid factor (RF) as immunoadsorbents. The effusions were first filtered through Sephacryl S-300 columns and the large mol wt material eluted in front of the IgG peak was used as the starting material, while most of the sera were processed without prior filtration. The IC eluted from the RF-coated tubes were radioiodinated and analyzed by electrophoresis on polyacrylamide gels, followed by autoradiography. Four putative IC-derived proteins were identified in the RF eluates and designated according to their mol wt (in Kdalton): p94, p46, p17 and p13. Protein94 was found in 1/8 BC effusions, but in none of the other samples tested; 'p46', which was actually a complex of several closely spaced proteins, was identified in at least 3/16 BC sera, 6/8 BC effusions, 3/4 OC effusions and 1/5 non-malignant effusions, but in none of 17 normal sera. The upper band of the complex seemed to be present mainly, if not exclusively, in effusions from patients with neoplasia. Protein17 and p13 were found more often and in higher concentrations in the malignant effusions. All of these proteins could be precipitated by treating the RF eluates with anti human Ig serum, suggesting that they were associated with Ig, presumably as immune complexes. (Author abstract) (35 Refs)

32. HUMAN CANCERS TRANSPLANTED IN NUDE MICE RETAIN THE EXPRESSION OF THEIR ORGAN-SPECIFIC NEOANTIGENS.

Thomson DM, Neville AM, Phelan K, Schwartz Scanzano R, Vandevoorde JP
Montreal General Hosp., Montreal General Hosp. Res. Inst., 1650 Cedar Ave., Montreal, Quebec H3G 1A4, Canada
Eur J Cancer Clin Oncol; 17(11):1191-1197 1981

Human cancers transplanted to nude mice seem to retain most features of the original tumor. To determine if organ-specific neoantigens were still expressed after transplantation, four different human cancers, supplied and coded by independent investigators, were assayed in the tube LAI assay. The LAI phenomenon measures the change in adherence properties of leukocytes that have bound an antigen to which they are sensitized immunologically. Four of four transplanted human cancers - pancreas, lung, breast, and colon - stimulated an LAI+ response with leukocytes from patients with cancers of the same organ. The antitumor response was not a vigorous against a pool of transplanted tumor extracts as against those prepared from liver metastases. Nonetheless, the results add to the mounting evidence that human cancers express neoantigens to which most humans bearing cancers respond immunologically. (Author abstract) (31 Refs)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

33. POSSIBLE ROLE OF ENDOGENOUS MMTV VIRUS IN CHEMICAL MAMMARY GLAND CARCINOGENESIS IN MICE.

Komarova EA, Kriukova IN
Lab. Immunology of Oncogenic Viruses, All-Union Cancer Res. Inst., Moscow, USSR
Biull Eksp Biol Med; 91(9):339-342 1981

The effect of immunization with inactivated endogenous MMTV virus on the yield of dimethylbenz(a)anthracene (DMBA)-induced mammary gland tumors was studied in BALB/c mice free of exogenous virus. The animals were first administered DMBA (1 mg/day, 1.5 mo, po); then, 1 wk later, they were immunized with formaldehyde-treated suspension of MMTV. Control mice were immunized with Moloney leukemia virus (MuLV). Mammary gland neoplasms were detected in 21% of the mice immunized with MMTV, compared with 39% of MuLV-immunized mice and 40% of nonimmunized mice. The av latent period of tumor development in the MMTV-immunized mice was 119 days, compared with 88 days in the MuLV-immunized mice and 82 days in nonimmunized mice. Indirect immunofluorescence analysis showed expression of gp52 and p27 viral antigens in tumor tissues from both the immunized and the control mice. (11 Refs) (In RUS)

RADIOLOGICAL ASPECTS OF MAMMARY GLAND CARCINOGENESIS

34. THE EFFECT OF DIFFERENT TYPES OF FLUORESCENT LIGHTING ON REPRODUCTION AND TUMOR DEVELOPMENT IN THE C3H MOUSE.

Chignell CF, Sik RH, Gladen BC, Feldman DB
Lab. Environmental Biophysics, Natl. Inst. Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC, 27709
Photochem Photobiol; 34(5):617-621 1981

The effects of cool-white (CW), pink (PK), and daylight-simulating (DS) fluorescent lights on the growth, lifespan, reproduction, and mammary tumor incidence were investigated in 26 male and 52 female C3H mice. By the end of the study (573 days), all female mice kept under the PK fluorescent light (234 microWatts/cm2 irradiance) and 97.5% of the females in each of the DS (425 microWatts/cm(2)) and CW (425 microWatts/cm(2)) had developed mammary tumors. The median tumor-development times were 51, 47, and 42 wk for the DS, CW, and PK groups, respectively. In all tumor nodules, the epithelial cells appeared to originate from the mammary gland. All tumors were diagnosed as adenocarcinomas or carcinomas. Prolactin is known to play a critical role in both the induction and growth of mammary tumors in rodents, suggesting that pituitary prolactin secretion could be affected by different lighting conditions. (23 Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

35. HYDROXYPROLINE AND ZINC EXCRETION IN PATIENTS WITH NEOPLASTIC BREAST DISEASE.

Percudani M, Dell'Anna B, De Lorenzis GF, Ferraccioli GF, Vaona GL
Istituto di Clinica Chirurgica 2, Universita degli Studi, Via Gramsci, 14, 43100 Parma, Italy
Int Surg; 66(3):233-236 1981

Hydroxyproline and zinc excretion were evaluated in 87 patients with neoplastic breast disease; 40 of these had carcinoma, without radiological and scintigraphy demonstration of bone metastases. In the group of patients with breast cancer, the mean values of hydroxyproline and zinc excretion were found to be significantly higher than in the group with benign breast disease: only 12 of the patients with histologically detected breast cancer had hydroxyprolinuria levels which were higher than the upper limit of the values obtained in the control group. The authors, therefore, conclude that the patients in this group must be considered as being at greater risk. (Author abstract) (12 Refs)

36. THE CYTOCHEMICAL DEMONSTRATION OF OESTROGEN RECEPTORS IN HUMAN BREAST CARCINOMAS.

Walker RA
Dept. Pathology, Univ. Leicester, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX, England
J Pathol; 135(3):237-247 1981

Presence of estrogen receptors (ER) in human breast carcinomas was examined. Eighty tissue samples from 79 patients (12 premenopausal and 67 postmenopausal) were studied by a cytochemical method involving two conjugation techniques (periodate and two-stage glutaraldehyde methods) to couple 17 beta-estradiol-6-O-carboxymethyloxime-bovine serum albumin with horseradish peroxidase. Compared with the 70% (56/80) detection rate of ER by the dextran-coated charcoal method (DCCM), 80% of samples (63/80) gave a positive reaction with the cytochemical method and all of those positive with the DCCM method were positive in the cytochemical study. Only seven samples were positive by histological examination. Nuclear staining was present in four samples. One was an infiltrating lobular carcinoma with few neoplastic cells and two were intraduct carcinomas. The periodate conjugation method led to a greater degree of coupling than the two-stage glutaraldehyde method even though a higher concentration was needed to demonstrate ER with the periodate method. Careful tissue preparation and handling are necessary for obtaining good results with the cytochemical method. (19 Refs)

37. THE SPECIFIC BINDING OF ANDROGENS AND THE SUBSEQUENT DISTRIBUTION OF ANDROGEN-RECEPTOR COMPLEXES WITHIN MCF-7 HUMAN BREAST CANCER CELLS.

MacIndoe JH, Woods GR, Lee FJ
Dept. Internal Medicine, Veterans Admin. Medical Center, Iowa City, IA, 52240
Steroids; 38(4):439-452 1981

Using a whole cell suspension assay technique, we have examined both the specific binding of testosterone (T) and dihydrotestosterone (17beta-hydroxy-5alpha-androstan-3-one) (DHT) and the subsequent distribution of androgen binding activity within MCF-7 human breast cancer cells. We have observed that both androgens are bound with high affinity to the same single class of receptor which is present at a concentration of approx 8,000 sites per cell. The incubation of cells with either T or DHT was followed by the nuclear accumulation of specifically bound ligand which increased to max values within 1 hr and then decreased thereafter. However, only about 30% of the total cellular specific binding activity observed with either androgen was localized within the nuclear compartment at any time during a 4 hr incubation. Further examination of the extranuclear binding component suggested that a substantial portion of this activity was localized to the particulate fraction of the cytoplasm. The results of these studies suggest that both T and DHT are capable of exerting biological activity within MCF-7 cells, and raise the interesting possibility that androgen-receptor complexes may participate in the direct regulation of mitochondrial and/or microsomal function in this system. (Author abstract) (15 Refs)

38. SHORT TERM ORGAN CULTURE OF HUMAN BREAST TUMOUR TISSUE AND ITS APPLICATION IN STUDIES OF STEROID METABOLISM.

Duncan JN, Davis JC, Wade AP, Walker S
Sub-Dept. Endocrine Pathology, Univ. Liverpool, Alder Hey Hosp., Liverpool L12 2AP, England
Eur J Cancer Clin Oncol; 17(10):1133-1142 1981

A method of organ culture capable of maintaining explants of human breast tumors for 3 days, as evidenced by comparison of the tumor histology before and after culture, is described. In general, survival was good, although cultures of scirrhous tumors were less successful. A commercial culture medium, Ham's F10, was used without serum addition but with the addition of insulin. Tumor tissue was cultured with 4-[14C]-cholesterol (11 cases), 4-[14C]-pregnenolone (3 cases) and 1beta,2beta-[3H]testosterone (3 cases). The existence of desmolase and aromatase enzyme systems in breast tumor tissue is suggested by the separation of neutral, acidic and phenolic fractions from cholesterol and pregnenolone cultures. Metabolites have not yet been identified. Further evidence of aromatase activity is given by the formation of [3H]-water from 1beta,2beta-[3H]-testosterone. (Author abstract) (31 Refs)

39. WHOLE-CELL UPTAKE AND NUCLEAR LOCALIZATION OF 1,25-DIHYDROXYCHOLECALCIFEROL BY BREAST CANCER CELLS (T47 D) IN CULTURE.

Sher E, Eisman JA, Moseley JM, Martin TJ
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Biochem J; 200(2):315-320 1981

Specific high-affinity receptors for 1,25-dihydroxycholecalciferol [1,25-(OH)2D3] have been described recently in broken-cell preparations of several cultured human breast cancer cell lines including the T47 D line. It was necessary to determine whether intact breast cancer cells in culture would bind 1,25-(OH)2D3 specifically and whether the next step in the proposed scheme of action, ie nuclear translocation, occurred. The following results were obtained. (1) Specific uptake of 1,25-(OH)2D3 by T47 D cells occurs in intact cells in culture. (2) The rate of uptake is proportional to medium 1,25-(OH)2D3 concentration but is slow compared with that of other steroid hormones, eg, estradiol, under identical conditions. Even at 0.5 nM-1,25-(OH)2D3 in the medium, at least 4 hr are required to reach max compared with less than 1 hr for estradiol binding. (3) Estimation of binding characteristics by Scatchard analysis indicates a single class of binding sites with Kd of 68 pM and 11,800 binding sites/cell, which are similar results to those obtained with broken-cell preparations. (4) Inclusion of various vitamin D metabolites in the incubation medium decreased specific binding of 1,25-(OH)2D3 by the intact cells in a manner identical with their effects in the broken-cell preparation and with potencies similar to their potency on Ca++ transport and bone resorption in vivo. Order of potency was 1,25-(OH)2D3 greater than (24R)-1,24,25-trihydroxycholecalciferol much greater than 25-hydroxycholecalciferol greater than (25R)-24,25-dihydroxycholecalciferol much greater than (25R)-25,26-dihydroxycholecalciferol. (5) In the 1,25-(OH)2D3-depleted state, 80% of the 1,25(OH)2D3 receptor is found in the cytosol fraction of the cells even when the subcellular fractionation is performed under low-salt conditions. By contrast after incubation with [3H]1,25-(OH)2D3, 59% of the specific 1,25-(OH)2D3 binding is found in the partially purified nuclei fraction. These data indicate that nuclear translocation of the receptor-hormone complex takes place in the intact T47 D cell. The results also support the hypothesis that the 1,25-(OH)2D3 receptor is functional in this cultured breast cancer cell line, which may provide a useful model for further study of the early biochemical events in 1,25-(OH)2D3 action. (Author abstract) (31 Refs)

40. GAMMA-GLUTAMYLTRANSPEPTIDASE: A TUMOR CELL MARKER WITH A PHARMACOLOGIC FUNCTION.

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Histochem J; 13(5):865-877 1981

The histochemical distribution of gamma-glutamyltranspeptidase (GGTP) in rat and human tissues is reviewed, and the changes observed during embryogenesis and carcinogenesis are discussed. The pattern of GGTP distribution is similar in both species, with activity in adults found primarily in the proximal tubules of the kidney, the secretory follicle cells of the pancreas, and the villous cells of th jejunum. There is only minimal activity in intestinal crypt cells, but considerable in mature villus cells. Mammary gland, bile duct cells in adult liver, endothelial cells of brain capillaries, follicle sheath cells in actively growing hairs, and lymphocytes also have associated GGTP activity. Higher activity is seen in both embryonal and cancerous tissues. Soon after initial exposure to carcinogens, islands of presumably preneoplastic cells form in the liver, and are characterized by very high GGTP activity. The majority of hyperplastic nodules and carcinomas that eventually develop also have increased GGTP activity. This induction of increased activity persists long after carcinogen exposure. The possible metabolic significance of GGTP is discussed. (63 Refs)

41. MODIFICATION OF FIBRONECTIN DISTRIBUTION PATTERN IN SOLID HUMAN TUMOURS.

Labat-Robert J, Birembaut P, Robert L, Adnet JJ
Laboratoire de Biochimie du Tissu Conjonctif (G.R. CNRS No. 40), Fac. Med., Univ. Paris-Val-de-Marne, 94010 Creteil, France
Diagn Histopathol; 4(4):299-306 1981

Fibronectin (FN) distribution (FND) in normal tissue and solid tumors was examined. Indirect immunofluorescence was used to analyze FND in normal breast tissues: FN was found on normal epithelial cell membranes, in periglandular and perivascular basement membranes, and in the intercellular stroma. In infiltrating breast carcinomas, cell membrane staining disappeared even before invasion, and the staining pattern of the glandular basement membranes became discontinuous and disappeared with invasion. Studies on FND in cancers of the bronchi, endometrium, prostate, thyroid, and urinary bladder revealed a loss of typical FND in the tissues. In sarcomas, the FND was considerably altered; loss of peric ellular labelling and decreased staining of FN in the extracellular matrix were observed. Immunofluorescence for FND may aid histological identification of atypical lesions and early malignant tumor invasion. (37 Refs)

42. LEVELS OF POLYAMINES AND NUCLEIC ACIDS IN HUMAN BREAST CARCINOMA.

Romano M, Cecco L, Cerra M
Istituto Tumori, Via Mariano Semmola, 80131 Napoli, Italia
Tumori; 67(5):431-435 1981

Polyamine and nucleic acid levels were determined in normal human breasts, in primary infiltrating ductal carcinoma breasts, in the uninvolved tissues of the same carcinoma-bearing breasts and in the urine of the same patients. The results showed that the production of polyamines in the carcinoma tissue is significantly higher than in normal tissue; the presence of a carcinoma in the breast does not modify the levels of polyamines and nucleic acids in the surrounding uninvolved tissue; spermidine and spermine are correlated both with DNA and RNA in the carcinoma; the urinary polyamine levels in the carcinoma-bearing patients were not significantly different from that of controls. There appeared to be a close relationship between polyamine biosynthesis and tumoral mammary cell development and a very fine control between the biosynthesis of both spermidine and spermine and nucleic acids. In addition, the localized solid breast carcinoma, with non-proven metastases, did not provoke an increase in polyamine excretion. (Author abstract) (25 Refs)

43. PRACTICAL APPLICATIONS OF IMMUNOCYTOCHEMISTRY TO THE PHARMACOLOGY AND TOXICOLOGY OF THE ENDOCRINE SYSTEM.

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Histochem J; 13(5):821-837 1981

Practical applications of immunocytochemistry in the investigation of endocrine glands and genital organs in pharmacologic and toxicologic studies are discussed. Using the immunoperoxidase technique and specific antisera, selective immunocytochemical staining can be localized in the various cell types found in the pituitary gland. Most hormones of the pars distalis and pars intermedia can be found in corresponding specific cell population. Diffuse hyperplasia and hypertrophy of either growth hormone or prolactin producing cells or both have been demonstrated immunocytochemically in the pituitarys of old dogs and estrogen and/or progestagen-treated Beagles. Using specific antisera and not labelled antibody peroxidase-antiperoxidase method, somatostatin was localized in a large population of immunoreactive neurons in the periventricular areas of the preoperative region and anterior hypothalmus of dogs. Using the immunoperoxidase technique and a specific antiserum against uteroglobulin, it has also been possible to localize specific staining in certain secretory cells of the rabbit endometrium in the preimplantation phase and after progesterone stimulation. Immunoreactive endogenous prolactin and growth hormone were detected in hyperplastic and neoplastic lesions of the dog prostate and mammary gland using the basic immunocytochemical procedure. Immunospecific prolactin and growth hormone staining was localized in different mammary tumors of the dog. Certain structural components of the mammary tumors, notably the myoepithelial elements and ductal epithelium, revealed predominant growth hormone-positive staining. These findings may explain the importance of growth hormone rather than prolactin in the pathogenesis of spontaneous and progestagen-related mammary tumors in the dog. (42 Refs)

44. PLASMINOGEN ACTIVATOR ACTIVITY AND COMPOSITION IN HUMAN BREAST CANCER.

Evers JL, Patel J, Madeja JM, Schneider SL, Hobika GH, Camiolo SM, Markus G
(c/o Markus) Dept. Experimental Biology, Roswell Park Memorial Inst., New York State Dept. Health, Buffalo, NY, 14263
Cancer Res; 42(1):219-226 1982

The plasminogen activator activity of human breast tumors was determined quantitatively in extracts of 33 primary tumors, 11 lymph node metastases, and 11 normal tissues. Activities varied more widely in the neoplastic tissues than in the normal ones. The mean activator content of the tumors (primary and metastasis) was significantly higher (p greater than 0.01) than that of normal tissues: 4.4-fold on a g wet tissue basis and 2.1-fold when the activities were referred to the protein content of the extracts. Primary and metastatic tumors were not significantly different from one another in their plasminogen activator content. In the six cases where tumors and normal tissue pairs from the same patients could be compared, the mean of the individual tumor:normal ratios was 10.0 (wet wt) or 3.6 (extract protein). In addition to the activator content, the molecular type of the enzymes was also determined, using goat antibody formed against human urinary urokinase as an inhibitor of activator activity. On the av, 80% of the activity of the tumor extracts could be inhibited by the antibody; extracts of normal breast tissue contained only 62% urokinase-like activator. The activators were also characterized by sodium dodecyl sulfate gel electrophoresis using two different methods for the zymographic visualization of activator bands. The fraction of urokinase-like enzyme determined by the fibrinogen copolymerization method agreed well with the results obtained by immunoinhibition. No correlation was found between activator activity or activator composition, on the one hand, and the degree of differentiation of the tumors, the fraction of positive lymph nodes found, or the amount of estrogen-binding protein (or their molecular size) in the cytosol of the tumors, on the other. This apparent lack of correlation may reflect variations in local physiological conditions which necessitate the presence of widely differing amounts of activator in order to ensure a critical amount of the product of the reaction catalyzed by this enzyme, ie, plasmin. (Author abstract) (37 Refs)

45. ALTERATIONS IN ELECTROPHYSIOLOGY OF CULTURED BALB/CFC3H MOUSE MAMMARY EPITHELIUM ASSOCIATED WITH NEOPLASTIC TRANSFORMATION.

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Cancer Lett; 14(3):237-242 1981

Prolactin-controlled transepithelial electrophysiological properties associated with the neoplastic state and with the presence of mammary tumor virus in BALB/cfC3H mouse mammary epithelium are described. Short-circuit current values from tumor-cell cultures were observed to be max 20% of prelactating cell culture values. Neoplastic epithelium potential differences were only slightly lower than in prelactating epithelium. Resistances of tumor-cell cultures were not different from those of prelactating cell cultures. The findings suggest a reduction in prolactin sensitivity with expression of mammary tumor virus. Such decreased prolactin sensitivity may result from differential effects of prolactin on the component elements of short-circuit current and resistance. (31 Refs)

46. HISTOCHEMICAL OBSERVATIONS ON ENZYMES IN PREGNANCY-DEPENDENT MAMMARY TUMORS OF GRS/A MICE.

Tsubura A, Ueda S, Shikata N, Morii S
Dept. Pathology, Kansai Medical Univ., Osaka 570, Japan
Acta Histochem Cytochem; 14(5):439-448 1981

Histochemical features of pregnancy-dependent mammary tumors in GRS/A female mice were compared with those of normal mammary glands of the same hosts and with those of pregnancy-independent mammary tumors. In maximally grown and regressing pregnancy-dependent tumors, succinate dehydrogenase, alkaline phosphatase, acid phosphatase, and glucose-6-phosphate dehydrogenase activities were lower than those in surrounding normal mammary glands. In the cytoplasm of some proliferating epithelial cells of ductal-like elements of maximally grown tumors, lactate dehydrogenase activity was similar to that in normal mammary glandular epithelium. Lactate dehydrogenase activity was high in epithelial cells lining microcysts of regressing mammary tumors, whereas activities of all other enzymes were decreased in these cells. Acid phosphatase activity was high in the necrotic foci within the regressing tumors, while other enzyme activities were not detected. In general, succinate dehydrogenase, glucose-6-phosphate dehydrogenase, acid phosphatase, and alkaline phosphatase activities were lower in pregnancy-independent mammary tumors than in surrounding normal tissue. Lactate dehydrogenase activity was variable in these tumors, but generally it was higher in malignant cells. (24 Refs)

47. ESTROGEN AND PROGESTERONE RECEPTORS IN BREAST CANCER.

Vihko R, Isotalo H
Dept. Clinical Chemistry, Univ. Oulu, SF--90220 Oulu 22, Finland
Acta Obstet Gynecol Scand [Suppl]; (101):29-35 1981

This review deals with measurements and properties of estrogen and progesterone receptors in human breast cancers, receptor frequency in primary and metastatic tumors and in pre- and postmenopausal patients, relationship between receptor status and serum hormone concentrations, receptor status and response to endocrine therapy, and receptor status as a prognostic factor both recurrence and survival. (67 Refs)

48. HORMONAL RECEPTORS OF ESTRADIOL AND PROGESTERONE IN MAMMARY CANCER.

Piffanelli A
Istituto di Radiologia, Universita di Ferrara, Ferrara, Italy
Radiol Med (Torino); 67(11):865-866 1981

Hormone receptors for estradiol and progesterone in mammary cancer are reviewed. The following aspects are discussed: methods of determination, standardization, location, type of bond, doses, and uses in hormone therapy or in combination hormone and chemotherapy. (7 Refs) (In ITA)

REVIEWS AND OTHER RELATED STUDIES

49. RETHINKING THE ENVIRONMENTAL CAUSATION OF HUMAN CANCER.

Higginson J
International Agency Res. on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 2, France
Food Cosmet Toxicol; 19(5):539-548 1981

Epidemiologic studies concerning the etiology of environmental cancers are reviewed. The results of a number of studies strongly suggest that most human cancers are related to environmental factors and not to racial or hereditary factors. The results of the author's survey in South Africa further suggested that 'way of life' was of major significance for many cancers, especially those of the gastrointestinal tract and endocrine-dependent organs. Although there are many factors involved in its etiology, cancer may be prevented by controlling a single predominant factor. Only a small part of the total cancer burden can be directly related to ambient environmental pollution, and a number of other environmental factors, particularly diet, must be considered for the majority of environmental cancers. Although the role of dietary factors in promotion and enzyme induction of cancers is well established in laboratory animals, their role in man is much less clear. Most epidemiologists do not consider human environmental cancers in terms of single causes; human cancers for which there is evidence of multistage and multifactorial origin include lung, esophagus, liver, stomach and large intestine, breast and endometrium, Burkitt's lymphoma, and nasopharyngeal carcinoma. (106 Refs)

50. BENIGN BREAST CONDITIONS.

Roses DF, Harris MN
Dept. Surgery, New York Univ. Sch. Medicine, New York, NY
Hosp Med; 17(11):114-115,119,122-123,126-127 1981

Discussion of benign breast disease, including signs, symptoms, diagnosis, and suggested treatment, is presented. Helpful means for distinguishing between benign and malignant breast disease include biopsy, patient and family history, age, frequency of pregnancies, and timing of menstruation in relation to examination. The presence of a mass during examination, along with changes in size or firmness of one breast, skin changes, nipple discharge, or changes in nipple epithelium, may provide information helpful to establishing diagnostic procedure. Fibrocystic disease ranging from epithelium-lined cyst to sclerosing adenosis presents with symptoms of breast discomfort. Histopathological changes include hyperplasia of duct epithelium, duct papillomatosis, and blunt duct adenosis. Treatment includes aspiration and re-examination or possibly mammography. When mammography is insufficient to distinguish from carcinoma, a biopsy is indicated. Mammary duct ectasia is characterized by a yellowish-brown discharge, thickening of the duct wall, and shortening and retraction of the nipple. Ductal excision is indicated; excisional biopsy should be performed if a mass is present. Intraductal papilloma presents with bloody nipple and should be further evaluated by biopsy and possibly mammography. Fat necrosis can sometimes mimic cancer; biopsy and mammography may be needed for definitive diagnosis. Fibroadenomas are solid, rubbery, movable lesions. Re-examination during another part of the menstrual cycle and excisional biopsy are indicated for diagnosis. Accurate diagnosis and patient reassurance are necessary when dealing with benign breast disease. (no Refs)

51. THE DECISION-POINT APPROACH FOR SYSTEMATIC CARCINOGEN TESTING.

Weisburger JH, Williams GM
Naylor Dana Inst. Disease Prevention, Valhalla, NY, 10595
Food Cosmet Toxicol; 19(5):561-566 1981

The decision-point approach provides a framework, based on current concepts of the mechanisms of carcinogenesis, for systematic evaluation of potential mutagenic and carcinogenic hazards of chemicals. Chemical carcinogens have been divided into two main categories-genotoxic agents, which interact with DNA and genetic material and lead to irreversible alterations in DNA, and epigenetic agents, which operate by distinct nongenotoxic mechanisms and are tissue-specific. Genotoxic agents include direct-acting carcinogens, procarcinogens, and inorganic carcinogens; the first two classes damage DNA either through direct chemical reactivity or following metabolism by enzyme systems, whereas inorganic carcinogens are not directly genotoxic but lead to changes in DNA by selective alteration in the fidelity of DNA replication. Epigenetic agents include solid-stage carcinogens, hormones, immunosuppressors, co-carcinogens, and promoters. The decision-point approach involves five steps: (1) consideration of the structure of the chemical; (2) in vitro short-term tests (mutagenesis, DNA repair, chromosome effects, and cell transformation); (3) limited in vivo bioassays (skin-tumor induction in mice, pulmonary-tumor induction in mice, breast-cancer induction in rats, induction of rodent liver altered foci, and assays for promoters); (4) chronic bioassay; and (5) final classification of a chemical as a genotoxic or epigenetic carcinogen. Health-risk analysis also must consider quantitative potential as well as qualitative positive or negative results. The proposed testing approach provides for systematic yet economical testing, the results of which can be applied to flexible, rational health-risk analysis. (26 Refs)

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Farber E

Dept. Pathology, Univ. Toronto, 100 College St., Toronto, ON M5G 1L5, Canada

N Engl J Med; 305(23):1379-1389 1981

2. N-HEXANE AND ITS TOXICOLOGIC EFFECTS. A REVIEW.

Jorgensen NK, Cohr KH

Harevaenget 44, DK-4200 Slagelse, Denmark

Scand J Work Environ Health; 7(3):157-168 1981

3. SAFROLE: ITS METABOLISM CARCINOGENICITY AND INTERACTIONS WITH CYTOCHROME P-450.

Ioannides C, Delaforge M, Parke DV

Dept. Biochemistry, Univ. Surrey, Guildford, Surrey GU2 5XH, England

Food Cosmet Toxicol; 19(5):657-666 1981

RADIATION CARCINOGENESIS

4. CARCINOGENIC, MUTAGENIC, TERATOGENIC WORKSHOP.

Suit H, Hall E, Frei E

Dept. Radiation Medicine, Massachusetts General Hosp., Boston, MA, 02114

Cancer Clin Trials; 4(Suppl):37-41 1981

5. DOSIMETRY OF THE ATOMIC BOMB SURVIVORS.

Sinclair WK, Failla P, Bond VP, Loewe WE, Kerr GD, Auxier J, Wyckoff OH, Maruyama T, Schull JW, Land EC, Dobson LR, Mays WC, Seymour J

Argonne Natl. Lab., 9700 South Cass Ave., Argonne, IL, 60439

Radiat Res; 88(3):437-447 1981

DIETARY FACTORS IN CARCINOGENESIS

6. NUTRITION AND CANCER: A REVIEW.

Muller E, Rickenbach M

Institut fur Sozial- und Praventivmedizin, Universitat Zurich, Gloriastrasse 32 B, 8006 Zurich, Switzerland

Praxis; 70(43):1903-1912 1981

In GER

7. FLAVONOIDS, MUTAGENS, AND CITRUS.

Horowitz RM

U. S. Dept. Agriculture, Agricultural Res. Service, Fruit and Vegetable Chemistry Lab., Pasadena, CA, 91106

ACS Symp Ser; 170:43-59 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

8. ETIOLOGICAL CONCEPTS IN CERVICAL CARCINOGENESIS.

Kessler II

Dept. Epidemiology and Preventive Medicine, Univ. Maryland Sch. Medicine, 655 West Baltimore St., Baltimore, MD, 21201

Gynecol Oncol; 12(2,part2):S7-S24 1981

9. CURRENT CONCEPTS ON THE AETIO-PATHOGENESIS OF ACUTE LEUKAEMIA.

Torres A, Martinez Guibelalde F, Gomez Garcia P, Garcia Castellano JM, Manzanares Escribano MR

Jefe Servicio Hematologia, Ciudad Sanitaria 'Reina Sofia' de la Seguridad Social, Cordoba, Spain

Sangre (Barc); 26(5B):700-717 1981

In SPA

10. CANCER FAMILY SYNDROME.

Svendsen LB, Bulow S

Kirurgisk-gastroenterologisk afdeling, Bispebjerg hospital, Copenhagen, Denmark

Ugeskr Laeger; 143(42):2713-2716 1981

In DAN

11. GENETIC AND BIOCHEMICAL STUDIES WITH ATAXIA TELANGIECTASIA.

Huang PC, Sheridan RB

Dept. Biochemistry, Sch. Hygiene and Public Health, Johns Hopkins Univ., Baltimore, MD, 21205

Hum Genet; 59(1):1-9 1981

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

12. THE HEALTH EFFECTS AND ECOLOGICAL SIGNIFICANCE OF CHLORINE RESIDUALS IN WATER.

Kalmaz EV, Kalmaz GD

Univ. Tennessee, Univ. Station 8163, Knoxville, TN, 37916

Chemosphere; 10(10):1163-1175 1981

13. CHEMICAL AND ENVIRONMENTAL AGENTS IN GASTROINTESTINAL CARCINOGENESIS.

Deschner EE, De Cosse JJ, Sherlock P

Lab. Digestive Tract Carcinogenesis, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021

Clin Gastroenterol; 10(3):755-771 1981

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14. THE REPAIR OF DNA DAMAGE: RECENT DEVELOPMENTS AND NEW INSIGHTS.

Friedberg EC, Bonura T, Love JD, McMillan S, Radany EH, Schultz RA

Dept. Pathology, Lab. Experimental Oncology, Stanford Univ., Stanford, CA, 94305

J Supramol Struct Cell Biochem; 16(1):91-103 1981

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15. ROLE OF HORMONES INCLUDING DIETHYLSTILBESTROL (DES) IN THE PATHOGENESIS OF CERVICAL AND VAGINAL INTRAEPITHELIAL NEOPLASIA.

Robboy SJ, Truslow GY, Anton J, Richart RM

Dept. Pathology, Massachusetts General Hosp., Boston, MA, 02114

Gynecol Oncol; 12(2,part2):S98-S110 1981

16. PROSTAGLANDINS AND CANCER: A REVIEW OF TUMOR INITIATION THROUGH TUMOR METASTASIS.

Honn KV, Bockman RS, Marnett LJ

Dept. Biological Sciences, Wayne State Univ., Detroit, MI, 48202

Prostaglandins; 21(5):833-864 1981

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17. GENITAL CANCER AND VIRUSES.

Rapp F, Jenkins FJ

Dept. Microbiology, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033

Gynecol Oncol; 12(2,part2):S25-S41 1981

18. VIRUS PAPILLOMAS IN HUMANS.

Nasemann T

Univ.-Hautklinik Eppendorf, Martinistr. 52, D-2000 Hamburg 20, W. Germany

Hautarzt; 32(11):601-606 1981

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PREVALENCE OF BREAST CANCER IN HUMAN POPULATIONS

1. EPIDEMIOLOGICAL REVIEW OF BREAST CANCER IN ISRAEL.

Katz L, Steinitz R, Sela T

Israel Cancer Registry, Ministry Health, 20 King David St., 94100 Jerusalem, Israel

Isr J Med Sci; 17(9/10):810-815 1981

Breast cancer is the most common malignant disease in women in Israel. Approx 1,000 new cases are diagnosed yearly. The peak incidence in all the population groups and periods observed is after the menopause. A steady increase in female breast cancer incidence was observed over a 17-yr period. The greatest increase occurred in the low-incidence group of Jews born in Asia/Africa. (Author abstract) (10 Refs)

2. BREAST CANCER IN ISRAEL. HISTOPATHOLOGIC TYPES IN THE DIFFERENT POPULATION GROUPS.

Sacks M, Selzer G

Dept. Pathology, Soroka Univ. Hosp., POB 151, 84101 Beersheba, Israel

Isr J Med Sci; 17(9/10):882-887 1981

The histological sections of 1,605 cases of breast cancer in Israeli women were examined to determine the frequency of the various histological subtypes in the different population groups. Infiltrating ductal carcinoma was the most common type in all groups. Circumscribed and medullary carcinoma were relatively less frequent among women born in North Africa than among immigrants from Europe or Asia. Invasive lobular carcinoma was very rare among women born in Asia. The findings are compared with those in other countries and discussed in relation to survival patterns in the different population groups in Israel. (Author abstract) (13 Refs)

3. MALE BREAST CANCER IN ISRAEL: SELECTED EPIDEMIOLOGICAL ASPECTS.

Steinitz R, Katz L, Ben-Hur M

Israel Cancer Registry, 2 King David St., 94100 Jerusalem, Israel

Isr J Med Sci; 17(9/10):816-821 1981

The 17-yr incidence of male breast cancer was analyzed from data of the Israel Cancer Registry for Jews and non-Jews, and for the Jewish subgroups of European/American-born and Asian/African-born. The 187 observed cases among Jewish males in Israel were compared with the 194 cases reported in the US Third National Cancer Survey and with female breast cancer rates for the same period. Results show that the dependence of male breast cancer (MBC) on the female rate seems to exist in both countries. The disputed observation of a higher rate of MBC among Jews is supported by the higher rates of MBC in Israel than in the USA. Data on the laterality and histological features of MBC are presented. The series included eight cases among non-Jews (Arabs). The ongoing survey of the Israel Cancer Registry revealed four families in which both husband and wife had breast cancer and one family with breast cancer in both father and son. (Author abstract) (25 Refs)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

4. CYSTIC BREAST DISEASE AS A RISK FACTOR TO BREAST CARCINOMA (MEETING ABSTRACT).

Veronesi U

Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy

International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

The definition of cystic disease suffers from lack of uniformity due to the criteria of individual pathologists. This is the main reason for the controversial data on the actuaria l risk of developing a breast carcinoma in patients with a cystic disease. Many studies based on the incidence of breast carcinomas in large groups of patients with cystic disease followed-up for a considerable number of yr give figures of the risk factor two or four x the risk in the general population. However, most of the series have been evaluated without statistical corrections. As a large number of patients with cystic disease are nulliparous, or had the first pregnancy late in life or belong to a high-income social class, the incidence of breast cancer must be corrected according to these additional risk factors. It must be moreover considered: 1) that a great proportion of women in the 10 yr preceeding the menopause have cystic lesions of the breast, 2) that the disease is a transitory one as it disappears at the menopause, 3) that the epithelium of the cysts is exceptionally the site of a cancerous growth. Cystic disease is not a major risk factor for breast cancer compared to other factors like family history, nulliparity, late first pregnancy. (no Refs)

5. EPITHELIAL DYSPLASIA IN NIPPLE ASPIRATES OF BREAST FLUID: ASSOCIATION WITH FAMILY HISTORY AND OTHER BREAST CANCER RISK FACTORS.

Petrakis NL, Ernster VL, King EB, Sacks ST

Dept. Epidemiology and International Health, Univ. California, 1699 HSW, San Francisco, CA, 94143

JNCI; 68(1):9-13 1982

Because of the strong association of epithelial dysplasia and breast cancer, the extent to which dysplasia of breast fluid epithelial cells obtained by nipple aspiration is associated with breast cancer risk factors was investigated. A significantly higher proportion of women who had a first-degree family history of breast cancer had dysplastic cells in breast fluid than women who had no such history. When family history status was correlated with various breast cancer risk factors, higher proportions of women with dysplasia were found among those who had a first degree family history of breast cancer and for whom certain other risk factors were present, which suggested additive and synergistic effects of these factors on breast epithelium. Breast epithelia of women with a first-degree family history of breast cancer may be more prone to abnormal differentiation in response to environmentally conditioned risk factors. (Author abstract) (28 Refs)

6. ENDOCRINOLOGIC ASPECTS OF BREAST CANCER RISK AND FIBROCYSTIC MASTOPATHY (MEETING ABSTRACT).

Tarquini B, Cecchettin M, Rosselli del Turco M, Cariddi A, Cavallini V, Nunnari G, Ciatto S

Ist Clin Med II, Cattedra di Semeiotica Medica, Univ Firenze, Florence, Italy

International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Fibrocystic disease of the human breast (FM) is obviously not a sufficient condition for the development of breast cancer (BC) because it is so common in comparison with the incidence of BC. Nevertheless FM is claimed to be a major risk factor involved in BC. A number of studies suggest that potential malignancy is related not only to histologic features but the other factors also intervene: 1) 14 women with histologically validated FM; 2) 14 women apparently healthy and without known risk factors (controi groups); 3) 4 women with known FM and very high risk for BC. On each serum sample, Prolactin, thyroid stimulating hormone (TSH), luteinizing hormone (LH) follicle stimulating hormone (FSH), Gastrin, 17-beta-estradiol, Calcitonin and parathyroid hormone (PTH) were evaluated by radioimmunoassay kits. Each subject was sampled during the intermenstruum. Seven patients with FM and 7 controls were sampled 4 x in a yr with selection of the season of sampling. Some FM patients showed differences in serum levels of Prolactin, TSH, LH and PTH suggesting changes in combined risk. These results and related ethical problems in very high risk women are discussed. (no Refs)

7. MULTIPLE PRIMARY CANCERS OF THE BREAST AND OVARY.

Prior P, Waterhouse JA

Cancer Epidemiology Res. Unit, Dept. Social Medicine, Univ. Birmingham, Birmingham, England

Br J Cancer; 44(5):628-636 1981

Multiple primary cancers of the breast and ovary were investigated as part of a survey being undertaken at the Birmingham and West Midlands Regional Cancer Registry. Population-based data relating to 17,756 registrations for breast and 3,470 for ovarian cancer between 1950 and 1964 were analyzed. On the basis of person-yr at risk and incidence rates for the Region (1960-1962), an increased risk of a second primary tumor in the ovary was observed in patients diagnosed with a first primary in the breast before 45 yr of age (O = 8; E = 1.83; p less than 0.001). No excess was found in patients diagnosed after 45 yr of age (O = 15; E = 17.06). In patients with an index tumor of the ovary, the observed number of second primary tumors of the breast was not significantly different from the expected number (O = 19; E = 12.95). Complementary analysis (a combined assessment for the 2 sites) showed that the development of a first primary at either site before 45 yr of age carried a 2.8-fold risk of a secondary primary tumor at the other site (O = 9; E = 3.21; p less than 0.01). After 45 yr of age no increased risk was found (O = 32; E = 28.63). Over all ages a 1.3-fold risk was observed (O = 42; E = 31.54; p less than 0.05). No evidence of subfertility was found in the nine patients in the high-risk premenopausal group who developed the two tumors. The results are more consistent with an etiology of early exposure to an external carcinogen than with one of abnormal hormone production. (Author abstract) (31 Refs)

8. AGE AT MENARCHE, PROBABILITY OF OVULATION AND BREAST CANCER RISK.

MacMahon B, Trichopoulos D, Brown J, Andersen AP, Aoki K, Cole P, DeWaard F, Kauraniemi T, Morgan RW, Purde M, Ravnihar B, Stormby N, Westlund K, Woo NC

Dept. Epidemiology, Harvard Sch. Public Health, 677 Huntington Ave., Boston, MA, 02115

Int J Cancer; 29(1):13-16 1982

An analysis is undertaken of the frequency of ovulation in 17 groups of women aged 15 to 19 who had been the subjects of other studies. A urine specimen of at least 8 hr accumulation had been provided on the 20th or 21st day of a menstrual cycle by 681 women. Analysis is restricted to 431 specimens which had been collected between 11 and 3 days prior to the onset of the subsequent menstrual period. A pregnanediol concentration of less than 1 mg/l in such a specimen was taken as evidence that the cycle was anovular. The probability of a cycle being anovular was inversely and significantly related to the number of yr since menarche, and, with yrs since menarche held constant, was positively but not significantly associated with age at menarche. This observation indicates that women with early menarche do not have a longer duration of exposure to anovular cycles than do those whose menarche is delayed, and that variation in the duration of exposure to post-menarcheal anovular cycles does not explain the association of breast cancer risk with early age at menarche. The 17 groups of women were classified into four categories according to ethnic origin and breast cancer incidence in the populations from which they derived. Anovular cycles were not more common in the high-risk groups; indeed, the two centers in the lowest risk category had the highest proportion of anovular cycles. (Author abstract) (15 Refs)

9. THE HORMONAL PROFILES IN BREAST CANCER: A STIMULATING TOPIC (MEETING ABSTRACT).

Marangolo M, Fiorentini GM, Baccini C

Oncologia Medica and Laboratorio Analisi, Ospedale Civile-Ravenna, Italy

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer, 131 pp., 1981.

The identification of some 'risk factors' for breast cancer suggests the possibility that these women should be carriers of a subclinical pathological endocrinologic condition that acts as promoting factor in the incidence of mammary tumors; aim of this work is to verify this possibility. One hundred post-menopausal breast cancer patients (pts), all free of disease with early bone or skin metastases, were studied in control conditons and after Metopirone test, for determination of plasmatic Estrone (E1), Estradiol (E2) and Testosterone (T) over a period of 72 hr and with total 13 blood samples each patient. It was possible to identify a subgroup with concentrations of E2 equal or superior to the mean + 1 standard deviation (named Hyper-E2 : 14 patients) and a normal subgroup (86 pt) with values of E2 inferior to the Mean + SD for each sample. With statistical analysis it was possible to establish that Hyper-E2 pt were also Hyper-E1, on the contrary there was not statistical difference in the values of T between the two subgroups. The linear regression analysis showed no correlation, statistically significant, between T/E1 or E/E2 in both subgroups; a strong correlation became evident between T/E2 only in the Hyper-E2 patients. These data suggest the possibility that there exists a percentage of women with major capacity to aromatize the androgenic steroids in Estradiol. (no Refs)

10. EPIDEMIOLOGIC STUDY OF DRINKING WATER CHLORINATION AND WISCONSIN FEMALE CANCER MORTALITY.

Young TB, Kanarek MS, Tsiatis AA
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JNCI; 67(6):1191-1198 1981

The association between gastrointestinal, urinary tract, brain, lung, and breast cancer mortality and drinking water trihalomethane exposure, as estimated by av daily chlorine dosage of water source 20 yr past, was investigated for Wisconsin white females by use of a death certificate-based case-control study design. A total of 8,029 cancer deaths and 8,029 controls (noncancer deaths) matched on county of residence, year of death, and age were taken from mortality records of 28 counties for the years 1972-77. Data on characteristics and treatment of municipal water supplied to the residences of cases and controls were obtained from questionnaires sent to the water superintendents of the 202 waterworks associated with the sample. By the use of logistic regression analysis, odds ratios for site-specific cancer death associated with high, medium, and low chlorine-dosed water as compared to unchlorinated water exposure were determined; the control variables were urbanicity, marital status, and occupation. With the exception of cancer of the colon, no anatomic cancer site was significantly associated with any chlorine dose exposure category. For colon cancer, odds ratios of 1.51 [95% confidence interval (CI) = 1.06-2.14], 1.53 (95% CI = 1.08-2.0) and 1.53 (95% CI = 1.11-2.11) were obtained for high-, medium-, and low-dose chlorination, respectively (p less than or equal to 0.02). For colon cancer cases and controls exposed to water sources affected by rural runoff, odds ratios of 3.30 (95% CI = 1.45-7.48), 3.60 (95% CI = 1.57-8.26), and 2.74 (95% CI = 1.10-6.88) were observed for high, medium, and low chlorine dosages 20 yr past (p less than 0.025). (Author abstract) (40 Refs)

11. MAMMOGRAPHIC PARENCHYMAL PATTERNS: RISK INDICATOR FOR BREAST CANCER?

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JAMA; 247(2):185-189 1982

Mammographic parenchymal patterns, originally presented as a new risk factor for breast cancer, have been prospectively studied in a large (27,157 examinations) consecutive screening population. Although there is a significantly higher risk of breast cancer in the so-called dysplastic breasts (P2 and DY pattern groups), the classification is of little practical value, as more than 72% of the cancers in the prevalent population were found in the so-called low-risk breasts (N1 and P1 pattern groups). A similar trend occurred at repeated screening of younger women, in which most of the 'incident' cancers were found in the 'low-risk' breasts. These patterns should not be used to influence patient management or screening programs. (Author abstract) (20 Refs)

12. MAMMOGRAPHIC PARENCHYMAL PATTERNS: MORE CONTROVERSY.

Moskowitz M
Breast Cancer Detection Center, Cincinnati, OH
JAMA; 247(2):210 1982

Disparate results in studies of mammographic parenchymal patterns as risk factors in breast cancer development are discussed, with emphasis on the P2/DY pattern. Current data do not justify use of parenchymal patterns to plan individual patient management or to develop strategies for mass screening. (7 Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

13. EARLIER APPEARANCE OF MURINE MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGENS IN DUCT-ALVEOLUS NODULES INDUCED BY TRANSPLANTATION OF FETAL SALIVARY MESENCHYME INTO C3H MOUSE MAMMARY GLANDS.

Sakaguchi S, Takahashi T, Sakakura T, Sakagami Y, Nishizuka Y, Tanaka H
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Gan; 72(6):982-987 1981

Mammary epithelium of adult C3H mice in contact with fetal salivary mesenchyme took morphogenetically a salivary gland-like pattern of growth and developed a hyperplastic nodular mass at the site of transplantation. When murine mammary tumor virus-bearing C3H mice were treated in this way, early development and high incidence of mammary cancer were observed from these nodules compared to unstimulated mammary glands of the same host. Since it is known that murine mammary tumor virus plays a major role in mammary tumor development, the viral antigens in these hyperplastic nodules were examined by means of the immunofluorescence technique. As early as 2 wk after mesenchyme transplantation, the antigens were observed in the ductular or alveolar structure of these nodules, while surrounding normal tissues were not stained. Positive fluorescence was also observed in the mammary tumors that developed from these stimulated nodules. These results strongly suggested the involvement of murine mammary tumor virus in the early development of mammary cancer induced by fetal mesenchyme transplantation. (Author abstract) (12 Refs)

14. COMPARATIVE METABOLISM OF 7,12-DIMETHYLBENZ(A)ANTHRACENE AND SEVERAL FLUORINATED ANALOGUES IN SYRIAN HAMSTER EMBRYO CELL CULTURE AND IN SPRAGUE-DAWLEY AND LONG-EVANS RATS IN VIVO.

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Diss Abstr Int [B]; 42(5):1844-B 1981

The metabolites resulting from the rat liver microsomal oxidation of 7-12,dimethylbenz(a)anthracene (DMBA) and its fluoro analogs were compared to the metabolites from treatment of Syrian hamster embryo (SHE) cell cultures with [3H]DMBA, [3H]2F-DMBA, [14C]5F-DMBA and [3H]11F-DMBA, SHE cells in culture were exposed to each of the above DMBA analogs up to 24 hr and the metabolites both within and outside the cell (in the media) were isolated and analyzed by high pressure liquid chromatography and fluorescence spectroscopy. Metabolites were also separated into their free and conjugated components by alumina chromatography and treated with either B-glucuronidase or sulfatase enzymes to identify their conjugated components. These studies were subsequently compared to the in vivo analysis of DMBA and 2F-DMBA in Sprague-Dawley and Long-Evans fifty day old, female rats. These two strains were chosen because of their sensitivity and resistance, respectively, to assult by DMBA and the subsequent development of mammary tumors. The DMBA and 2F-DMBA metabolites isolated from the urine of these rats were analyzed using similar techniques as those described above for the SHE cell metabolism. Several differences between the two species were noted. (no Refs)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

15. MODIFICATION OF MAMMARY CARCINOGENESIS AND TISSUE PEROXIDATION BY SELENIUM DEFICIENCY AND DIETARY FAT.

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Dept. Breast Surgery and Breast Cancer Res. Unit, Roswell Park Memorial Inst., Buffalo, NY
Nutr Cancer; 2(3):136-142 1981

The independence of selenium (Se) and unsaturated fat intake as modifiers of the incidence of mammary tumors induced by 7,12-dimethylbenz(a)anthracene (DMBA) and the liability of mammary tissue to lipid peroxidation were studied. Female Sprague-Dawley rats were fed one of six synthetic diets (three different types of diets with and without Se supplementation) from weaning until termination of the experiment. The three basal diets contained different levels of tocopherol-stripped corn oil, 1%, 5%, and 25%. Mammary tumors were induced by intragastric administration of a 5 mg dose of DMBA at 50 days of age. Measurement of Se-dependent glutathione peroxidase activity in the rat liver was used to determine the functional status of Se at 0, 10, 20, and 30 days after the rats were given either the basal Se-deficient diet or the supplemented regimen. In rats receiving an adequate supplement of Se (0.1 ppm) tumor incidence increased proportional to the amount of corn oil in the diet. A deficiency of Se in the diet resulted in a marked enhancement in tumor incidence and yield in rats fed the 25% corn oil regimen. Glutathione peroxidase activity in the mammary gland was not influenced by dietary fat but was severely depressed in the absence of added Se. Lipid peroxidation in the mammary tissue was elevated with increasing levels of dietary fat in rats supplemented with 0.1 ppm of Se. The unsupplemented 25% fat group showed significant enhancement of tissue peroxidation when compared to their supplemented controls. Determination of peroxide in the synthetic diets demonstrated that corn oil when mixed with the other ingredients, auto-oxidized very quickly especially at room temperature. The amount of peroxide formed is proportional to the content of corn oil and to the length of storage. Se deprivation did not affect the tumor growth rate or the proliferation of malignant vs benign lesions. (40 Refs)

16. INFLUENCE OF PRENATAL EXPOSURE TO DIETHYLSTILBESTROL ON ESTROGEN AND PROGESTIN BINDING PROTEINS IN UTERI AND DIMETHYLBENZANTHRACENE-INDUCED MAMMARY TUMORS OF THE RAT.

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J Toxicol Environ Health; 8(4):667-686 1981

Various characteristics of steroid binding proteins from mammary tumors and from uteri of rats exposed prenatally to diethylstilbestrol (DES) were examined. Pregnant rats were treated with no hormone (group A) or with a total dose of 1.2 ug DES during the second (group B) or third (group C) trimester of gestation. Female offspring received 7,12-dimethylbenz(a)anthracene (DMBA) at day 50 +-1. Animals with large mammary tumors were subjected to bilateral ovariectomy. The experiment was terminated 7 mo after carcinogen treatment. High-affinity binding sites for (3H)estradiol-17beta and (3H)R5020 were found in all mammary tumors assayed. Estrogen receptor forms 8S and 4S were identified on sucrose gradients of low ionic strength regardless of prenatal treatment. Progestin receptors (PR) sedimenting at 4S were also identified in the tumors. PR form 7-8S was found only in tumors from intact animals. PR levels diminished after ovariectomy in mammary tumors and in uteri. Uterine progestin binding capacities and uterine wet wt did not decrease proportionally after ovariectomy in group C. PR capacities in mammary tumors from group C were higher than in other groups. Cytosol from mammary tumors in group C intact rats also had elevated PR levels. Uterine estrogen binding capacities did not vary significantly. Prenatal exposure to DES during the third trimester appeared related to persistent biochemical alterations in rat mammary tumors and uteri. Earlier exposure did not have the same effect. (61 Refs)

17. SIALIC ACID METABOLISM IN NUTRITIONALLY MODULATED MAMMARY GLAND CARCINOGENESIS.

Fox OF, Kishore GS, Carubelli R
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Cell Mol Biol; 27(5):473-482 1981

The activities of CMP-N-acetylneuraminic acid synthetase, sialyltransferase and neuraminidase were investigated in female Sprague-Dawley rats with mammary adenocarcinomas induced by oral administration of 7,12-dimethylbenz[a]anthracene. The carcinogenic process was modulated by the levels and degree of unsaturation of the dietary lipids in the presence and in the absence of dietary antioxidants. The activities of the biosynthetic enzymes responsible for the activation and transfer of sialic acids, ie CMP-N-acetylneuraminic acid synthetase and sialyltransferase were higher in tumors than in control mammary glands. The cytosolic and membrane-bound neuraminidases, on the other hand, were higher in control tissue than in tumors. In the low-fat dietary group, which had the lowest rate of tumor incidence, a tocopherol effect on sialic acid metabolism was detected; rats fed low-fat diet supplemented with alpha-tocopherol exhibited the highest levels of control mammary gland sialyltransferase activity, whereas tocopherol deficiency was accompanied by a loss of the tumor-dependent enhancement of CMP-N-acetylneuraminic acid synthetase. The enzyme profiles in the livers of control and tumor-bearing rats, although less well defined, showed some of the general trends observed in mammary tissues. (Author abstract) (21 Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

18. HORMONE LEVELS IN HUMAN BREAST CYST FLUID (RELATIVE PLASMA CYST FLUID LEVELS) AND STUDIES ON THE MECHANISM OF ENTRY OF HORMONES INTO BREAST CYSTS (MEETING ABSTRACT).

Bradlow HL, Schwartz MK, Fleischer M, Rosenfeld SS, Kream J, Breed CN, Fracchia AA
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International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Cyst breast disease is a common occurence in women from age 35 to menopause. Although breast cysts are not precancerous per se, repeated studies over many yr have reported an increased risk for breast cancer in women with breast cysts when compared to normal controls. As part of a program to explore the possible relationship between the unusual hormone levels found in breast cyst fluid and the incidence of breast cancer, the concentration of a wide variety of hormones in breast cyst fluid were determined and compared with the plasma levels of these same compounds. Hormone levels were measured in cyst fluid from 1046 women who were then followed to determine breast cancer incidence. Both peptide and steroid hormones were measured in cyst fluid and in blood samples obtained simultaneously. The peptide hormones measured were luteinizing hormone (LH), follicle stimulating hormone (FSH), human prolactin (HPrL) and beta human chorionic gonadotropin (beta HCG). The first two compounds were present in cyst fluid in concentrations at or below plasma concentrations. HPrL and betaHCG however, were present in cyst fluid at concentrations greater than the plasma concentration in most of the patients studied. The cyst/plasma ratio ranged from only slightly greater than 1 to 200-fold. No correlation was found between the magnitude of the HPrL level and the betaHCG levels. The steroids studied were cortisol (F), testosterone (T), dihydrotestosterone (DHT), progesterone (P), estradiol (E2), estrone (E2), dehydroisoandrosterone (D), androsterone (A), and the sulfates of the latter four compounds. F, T, P. DHT, E1 and E2 were not significantly elevated in cyst fluid over plasma levels. D, A, DS, AS, E1S and E2S all showed elevated cyst fluid/plasma ratios, indeed in some cases as much as several thousand-fold greater than . Levels of DS and AS were as high as 20000 ug/dl. E1S and E2S were also markedly elevated in cyst fluid. (no Refs)

19. FECAL STEROID EXCRETION IN BENIGN BREAST DISEASE - SIMILARITIES TO BREAST CANCER (MEETING ABSTRACT).

Papatestas AE, Miller SR, Panveliwalla D, Aufses AH
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International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

The observed association between benign breast disease and breast cancer risk suggests a possible common etiologic mechanism. Fecal steroid levels have been linked to breast cancer risk through enhancement of estrogen synthesis from cholesterol metabolites. We have measured fecal steroids in women with breast cancer (cases) and in control women with or without benign breast disease (BBD). The former control group includes women with fibrocystic disease, intraductal papillomas, sclerosing adenosis and fibroadenomas. Three fecal specimens per patient were collected at the time of diagnosis and treatment, and the mean steroid value was evaluated. Determination of steroid levels in mg/g dry wt was made by the methods of Grundy and Miettinen. Comparison of the mean excretion of fecal steroids between controls with or without benign breast disease and cases, using analysis of variance showed significant differences for all neutral steroids but not for acidic steroids. The results indicate that women with benign breast disease have increased excretion of fecal steroids similar to that of cases but significantly higher than that of the remaining controls. T test for differences between groups (1) and (2) for total fecal steroids (TFS) equals p less than 0.01, for total neutral steroids (TNS) equals p less than 0.02, for first NS equals p less than 0.05, for second NS equals p less than 0.1. For total bile acids (TBA) there was no significant difference between groups (1) and (2). Women with fibrocystic disease did not seem to have high fecal steroids when compared to women with other types of benign breast lesions. Variations in degree of obesity between the three groups could not account for the observed differences as these persisted even among the subgroups of lean women. The findings support the concept of a common etiologic mechanism between benign and malignant breast lesions which seems to be linked to increased cholesterol synthesis and degradation in these two entities. (no Refs)

20. HORMONE REGULATION OF DNA SYNTHESIS OF NORMAL AND HYPERPLASTIC HUMAN BREAST TISSUES IN VITRO AND IN VIVO (MEETING ABSTRACT).

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International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

The hormones analyzed in these studies were bovine insulin (5.0 ug/ml), ovine prolactin (5.0 ug/ml), human prolactin (5.0 ug/ml), human placental lactogen (5.0 ug/ml), human growth hormone (5.0 ug/ml), 17beta-estradiol (0.001 ug/ml) and progesterone (1.0 ug/ml). Epithelial (ductal) DNA synthesis of the cultured human breast tissues was significantly stimulated by insulin, human prolactin, human placental lactogen and 17beta-estradiol; ovine prolactin, human growth hormone and progesterone were without a stimulatory effect. The original morphology of the explants was maintained. In vivo studies (athymic nude mice): Human breast tissue was obtained and processed as described above and transplanted sc (dorsal) to 8 wk old female athymic nude mice (Balb/c). Thirty days after transplantation, the mice were treated with the following hormones: human placental lactogen (0.5 mg; 2 x daily); estrogen (17beta-estradiol, 1.0 ug, 1 x daily and estrone in drinking water, 0.5 mg/liter) or a sc grafted rat pituitary tumor (RPT) which secretes copious quantities of prolactin and growth hormone (host mice blood rat prolactin levels, greater than 4000 ng/ml). After 30 days of hormone treatment, the grafted human breast tissues were excised and incubated for 4 hr in a 3H-thymidine enriched culture media. The grafts were processed for 3H-thymidine autoradiography. Human placental lactogen, estrogen and estrogen + RPT significantly stimulated DNA synthesis of the ductal epithelium of the grafted human breast tissues; RPT alone was ineffective. One hundred percent of the grafts were accepted by control or hormone treated mice; no sign of immunological rejection was observed. The grafts acquired the host blood supply and retained the original morphology. The relative merits of our in vitro and in vivo systems for the study of human breast tissues will be discussed. (no Ref s)

21. PLASMA PROLACTIN LEVELS IN PATIENTS WITH BREAST CANCER.

Rose DP, Pruitt BT
Div. Clinical Oncology, Wisconsin Clinical Cancer Center, 600 Highland Ave., Madison, Wisconsin, 53792
Cancer; 48(12):2687-2691 1981

The plasma prolactin levels of 98 healthy women 22 to 65 years old showed a strong inverse correlation with age. This relationship persisted for older premenopausal and postmenopausal women (aged 30 to 65 years) whose results were compared with those of 34 premastectomy early breast cancer patients, another 38 studied 4 to 6 weeks after mastectomy, and 38 with advanced disease (age range, 30 to 77 years). There was no correlation between age and plasma prolactin in any of the breast cancer groups. When patients and controls were classified according to their menopausal status, the premastectomy and postmastectomy early breast cancer groups both showed significantly higher prolactin concentrations than the corresponding controls (p less than 0.001 in all cases). These abnormalities were particularly prominent in the patients studied after surgery, although the difference was significant only for the postmenopausal groups (p less than 0.05). Plasma cortisol and urinary free cortisol levels were normal in postmastectomy patients, suggesting that stress was not the cause of elevated prolactin levels. In advanced breast cancer, elevated plasma prolactin concentrations were found only in the postmenopausal patients. (Author abstract) (32 Refs)

22. SERUM CONCENTRATIONS OF TOTAL AND NON-PROTEIN-BOUND OESTRADIOL IN PATIENTS WITH BREAST CANCER AND IN NORMAL CONTROLS.

Moore JW, Clark GM, Bulbrook RD, Hayward JL, Murai JT, Hammond GL, Siiteri PK
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Int J Cancer; 29(1):17-21 1982

In premenopausal women with breast cancer, total serum estradiol (E2) concentrations are normal, but nonprotein-bound E2 concentrations are significantly raised. This is not due to low sex-hormone-binding-globulin (SHBG) binding capacities, which are within the normal range, and is unlikely to be due to the small but significant decrease in albumin concentrations. In post-menopausal patients, both total and non-protein-bound E2 are significantly raised; this may be explained partially by lower SHBG binding capacities. In patients and controls there is a highly significant correlation between non-protein-bound E2 and SHBG, but for a given SHBG binding capacity, the patients have more non-bound E2 than controls. It is concluded that the breast in women with breast cancer may be exposed to elevated levels of biologically active E2, although the reasons for this remain obscure. (Author abstract) (19 Refs)

23. DISTRIBUTION OF PROSTAGLANDINS B, E AND F SERIES IN PLASMA OF CANCER PATIENTS.

Harvey PR, Kimura LH, Cripps C, Hokama Y
Univ. Toronto, Toronto, Canada
J Med; 12(6):427-432 1981

Plasma prostaglandins (PGs) of normal individuals and cancer patients have been examined. With the exception of a breast carcinoma patient, all patients demonstrated significant elevations in PGE levels. Lung cancer patients showed a significant decrease in PGF, while stomach cancer patients showed a marked decrease in PGB. It is suggested that the changes in PGs may play a significant role in host-tumor metabolism. (Author abstract) (8 Refs)

24. PROSTAGLANDIN E2 AND CYCLIC AMP IN TUMOR AND PLASMA OF BREAST CANCER PATIENTS.

Malachi T, Chaimoff C, Feller N, Halbrecht I
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J Cancer Res Clin Oncol; 102(1):71-79 1981

Prostaglandin E2 and cyclic AMP (cAMP) levels were measured in tumors and plasma of 78 patients with benign and malignant breast tumors. Two groups of malignant tissues were found, one with a high level of PGE2 (M = 55.4 pg/mg) and one with a low level (M = 10.7 pg/mg). The low level did not differ significantly from the benign tissue level (M = 8.7 pg/mg). Two malignant groups could not be detected in the plasma levels. Plasma PGE2 concentration (in form of the 13,14-dihydro-15-Keto metabolite) did not reflect the tissue levels, and no difference was found between the benign (M = 59.9 pg/ml) and the malignant (M = 62.3 pg/ml) patients, but both concentrations were higher than those of healthy controls (M = 34.4 pg/ml). The stage of the cancer, the histological classification and, most important, the period of survival, could not be related to the differences in the PGE2 tissue levels. Neither could plasma cAMP be nominated as a breast cancer marker because no difference was found between the cAMP levels of benign tumor patients (M = 16.48 pmol/ml), of malignant tumor patients (M = 21.24 pmol/ml) and of healthy controls (M = 19.07 pmol/ml). The conclusion is that although high amounts of PGE2 appear in some malignant breast tumors, they do not affect the clinical situation. These results may explain the failure to treat human breast cancer patients with prostaglandin synthetase inhibitors. (Author abstract) (28 Refs)

25. HORMONAL PATTERN AND SEX HORMONE BINDING GLOBULIN IN PLASMA OF WOMEN WITH CYSTIC BREAST DISEASE (MEETING ABSTRACT).

Berta L, Frairia R, Bumma C, Navello C, Mossetti C, Rovero E, Gaidano G
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International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Fibrocystic mastopathy is a benign disease of fertile women, considered as a clinical condition at high risk for breast cancer. Etiopathogenesis is still uncertain but often the clinical on set has been related to plasma sex hormone imbalance. Sex Hormone Binding Globulin (SHBG) could be also involved. Recently SHBG has been hypothized to play a significant role in breast cancer development. The aim of present work was to study plasma hormonal pattern (E1; E2; P; prolactin, PRL) with respect to Sex Hormone Binding Globulin binding capacity (SHBG-bc) in fertile women with fibrocystic breast disease. In plasma of 57 women with fibrocystic breast disease (aged 18-42 yr) and of 30 normal control women (aged 21-45 yr) the following parameters have been evaluated: E1, E2, P, PRL by radioimmunoassay (RIA) (Biodata); SHBG-bc by an equilibrium partition technique (PEG/Dextran). All subjects were studied in the luteal phase of the menstrual cycle: they had body wt in normal range and were free from endocrinological, hepatic or renal diseases. Progesterone plasma levels significantly lower in patients than in controls are according to the data observed by Mauvais-Jarvis et al and confirm the hypothesis that altered ratio Estrogens/Progesterone interferes in the onset of the disease. Estradiol-17-beat and estrone plasma levels in our cases do not show significant difference, but SHBG-bc is lower in the patients than in normal subjects. These data support that Progesterone and SHBG-bc deficiency respectively induce a relative increase of estrogen plasma levels, influencing mammary epithelium proliferation. (no Refs)

26. PROGESTERONE INSUFFICIENCY IN BENIGN BREAST DISEASE (MEETING ABSTRACT).

Kuttenn F, Fournier S, Sitruk-Ware R, Martin PM, Mauvais-Jarvis P
Service d'Endocrinologie, Hopital Necker, Paris, France
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

That the different clinical expressions of benign breast disease are due to an ovarian dysfunction. Evidence for this was found in an investigation of 184 patients with various benign breast diseases (permanent mastodynia, fibroadenomas, cystic mastitis and fibrocystic disease). In all these patients the luteal plasma progesterone to estradiol ratio was found to be significantly lower than in normal women. In vitro: estradiol and progesterone receptors were found in fibroadenomas with high epithelial cell density and no fibrosis. In the case of old lesions with low cell density and extensive fibrosis, no receptors were found. Cytosolic and nuclear estradiol and progesterone receptors were also studied in fibroadenomas of high cellular density according to the phase of the menstrual cycle. Cyclic changes in level and distribution of these receptors were similar to those noted in the human endometrium: the highest levels were found in the late follicular phase, whereas both estradiol and progesterone receptors decreased in the luteal phase. Moreover, the correction of luteal insufficiency by progestagen treatment induces a translocation of the progesterone receptor from the cytosol to the nucleus, which warrants the efficiency of such a treatment. (no Refs)

27. STEROID HORMONE RECEPTORS AND PROSTAGLANDIN SYNTHESIS IN BENIGN BREAST DISEASES (MEETING ABSTRACT).

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International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Studies on steroid receptor (SR) and prostaglandin (PG) synthesis in benign breast disease, from our viewpoint, are involved in further characterizing mechanisms of hormone cancerogenesis and tissular-hormone dependence of breast cancer in humans. Particularly, we have previously presented evidence suggesting that an elevated PG production is a marker of high metastatic potential for neoplastic mammary cells due to the improvement of the cellular autonomy which is concomitant to the loss of tissular-hormone dependence for these cells. When measured in both phases of the menstrual cycle of women suffering from benign mastopathies, plasma levels of both estradiol (E2) and progesterone (P) were lower in patients than in control women, resulting in an hormone imbalance with a relative excess of estrogen whose magnitude varies according to the individual degree of deficiency of P and E2. In both phases of the cycle, PGE blood levels were significantly higher in patients with benign mastopathies than in normal women. At the lesion's level, PG production was observed to be higher in benign disease than in normal breast. An estrogen-directed synthesis of PG is proposed to occur concomitantly to the benign epithelial hyperplasia induced by hormone imbalance. Similar results concerning estrogenic regulation of PG synthesis was observed in breast cancer. Both estrogen receptor (ER) presence and content increase as epithelial cell hyperplasia does in benign breast disease. A significant level of ER-PR couple appears in the lesions exhibiting lobular and ductal hyperplasia. Moreover, each lesion of high-intensity hyperplasia, ie diffuse ductal and lobular cell proliferation and hyperplasia associated or not with multiple papilomas, was found to be ER-PR positive while ER-PR couple was not detected in lesions in which fibrocystic alterations were associated with fibrosing adenosis. (no Refs)

28. EFFECT OF AN LHRH ANALOG ON GROWTH AND HORMONE RECEPTOR LEVELS IN DMBA-INDUCED MAMMARY TUMORS IN THE RAT.

Turcot-Lemay L, Cusan L, Seguin C, Kelly P, Labrie F
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J Recept Res; 2(2):135-151 1981

Hormone-dependency of dimethylbenz(a)anthracene (DMBA)-induced mammary tumors in rats was studied. Daily injections of luteinizing hormone-releasing hormone (LHRH) agonist, [D-Ala(6), des-Gly-NH2(10)]LHRH ethylamide (LHRH-A), 1 ug/day, for 38 days resulted in a 35% decrease in the number of tumors present at the start of the experiment compared to decreases of 45% after ovariectomy and of 8% in the control group. Although LHRH-A administration resulted first in a stabilization in the number of tumors, a marked inhibitory effect of the LHRH agonist on total tumor mass/rat was observed. There was marked reduction in ovarian luteinizing hormone (LH) and follicle-stimulating hormone (FSH) receptors while prolactin receptors were unchanged. Estrogen and progesterone receptor levels decreased after ovariectomy but treatment with LHRH-A had no significant effect on these receptors. Plasma LH and FSH levels increased after ovariectomy. Treatment with LHRH-A was followed by similar but less marked increases in plasma LH and FSH, with significant decrease in plasma prolactin and progesterone levels. The mechanisms by which LHRH-A induces the antitumor effect probably is related to desensitization of the ovary to LH and FSH with a concomitant decrease in circulating levels of estrogen and prolactin. (21 Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

29. IMMUNE COMPLEX-LIKE MATERIALS IN SERA OF PATIENTS WITH BREAST CANCER: DETECTION BY COMPLEMENT-CONSUMPTION ASSAY.

Sulitzeanu D, Asaf O, Biran S, Brufman G, Gilead Z
Lautenberg Center General and Tumor Immunology, Hebrew Univ.-Hadassah Medical Sch., POB 1172, 91120 Jerusalem, Israel
Isr J Med Sci; 17(9/10):869-873 1981

Sera of patients with breast cancer were tested for the presence of immune complexes by a complement-consumption assay. To increase the concentration of immune complexes and thus improve the chances of their detection, sera were first ultracentrifuged and the sedimented material was assayed. Sera were considered to be positive if they consumed at least 75% of the hemolytic activity under the conditions of the test. Of the 60 patients tested, 45% were positive as compared with 13.5% positive sera among healthy blood bank donors. The presence of immune complexes could not be correlated with the extent of disease, the age of the patients, treatment or lack of treatment at the time of the test, or the time that had elapsed since diagnosis. In a few control tests, treatment of samples with DNase had no effect on their anticomplementary activity, whereas reduction with 2-mercaptoethanol abrogated the activity. These results strengthened the assumption that the substances binding complement were indeed immune complexes. (Author abstract) (19 Refs)

30. SERUM IMMUNOGLOBULINS IN CARCINOMA OF VARIOUS ORGANS.

Gupta SC, Shukla HS, Sinha SN, Kumar S
Dept. Pathology and Surgery, M.L.N. Medical Coll., Allahabad, India
Indian J Cancer; 18(4):277-281 1981

Pre- and post-operative levels of serum immunoglobulins (SIgs) were investigated in 129 patients with carcinoma of a variety of organs. Samples of blood were taken one day before and 10-14 days after resection of tumor. In patients with benign breast disease, no significant change in different Ig values was observed in comparison to healthy controls. Of 37 cases of breast carcinoma, 5 were in stage I, 17 in stage II, and 15 in stage III. SIgs were not altered in Stage I pre- or post-operatively. With progression of the disease to stage II, IgA was found to be significantly increased wherease IgG was decreased IgM was within the normal range. Ten-14 days postoperatively, IgA decreased to control levels. In stage III disease, the stage II pattern was followed, but with greater intensity. In stomach cancer IgA and IgG and in colorectal cancer IgA and IgM were significantly increased. Increased IgG in stomach cancer patients returned to normal on the tenth postoperative day. Serum IgA was significantly increased in all 51 patients with carcinoma of the oral cavity. IgG was increased in carcinoma of the cheek, jaw and larynx. (23 Refs)

31. LOCAL IMMUNOGLOBULIN A IN NORMAL AND NEOPLASTIC BREAST TISSUES.

Lee PP, Buehring GC
(c/o Buehring) Dept. Biomedical and Environmental Health Sciences, Univ. California Sch. Public Health, Berkeley, CA, 94720
JNCI; 67(6):1231-1239 1981

Local IgA levels in 36 normal, 92 nonmalignant atypical, and 47 malignant human breast tissue specimens were analyzed by three methods: direct immunofluorescence, modified radioimmunoassay for IgA in cryostat sections, and the Immuno-Fluor (Bio-Rad Laboratories, Richmond, Calif) assay for the cell surface IgA in tissue eluates. The proportion of epithelium in each sample was estimated microscopically. For malignant specimens the proportion of epithelial cells was significantly higher than that for nonmalignant specimens. The immunofluorescence test showed no qualitative difference in epithelial IgA content between normal and nonmalignant atypical tissues, but the frequency of positive specimens were markedly lower in malignant tissues. The modified radioimmunoassay and the Immuno-Fluor assay indicated little or no difference in IgA concentration per tissue wt among normal, nonmalignant atypical, and malignant breast tissues. However, when the data were corrected for proportion of glandular epithelium, nonmalignant atypical tissues had less IgA per cell than normal tissues, and malignant mammary carcinomas had significantly less IgA per cell than both normal and nonmalignant atypical tissues. (Author abstract) (24 Refs)

32. ANTI-POLY(A) POLYMERASE ANTIBODIES IN SERA OF TUMOR-BEARING RATS AND HUMAN CANCE R PATIENTS.

Stetler DA, Rose KM, Jacob ST
Dept. Pharmacology and Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Pennsylvania State Univ., Hershey, PA, 17033
Proc Natl Acad Sci USA; 78(12):7732-7736 1981

Poly(A) polymerase (polynucleotide adenylyl-transferase; ATP:polynucleotide adenylyltransferase, EC 2.7.7.12) was covalently linked to diazobenzyloxymethyl-filters and used to screen the sera from a number of tumor-bearing rats and human cancer patients for antibodies to poly(A) polymerase. Sera from rats that had been inoculated with any of several Morris hepatomas or a mammary adenocarcinoma contained immunoglobulins capable of complexing with poly(A) polymerase. No antibodies to the enzyme could be detected in sera from control animals or from those bearing tumors for short periods of time. Antibodies to poly(A) polymerase were also observed in sera from human patients with leukemia, polycythemia vera, and Wilms tumor. The antibodies were not evident in sera from normal volunteers or from patients with nonneoplastic diseases. These included lupus erythematosus, a disorder in which antibodies are produced against an array of nuclear proteins. Immunoglobulins from the serum of one of the human patients were capable of inhibiting poly(A) polymerase activity in vitro, whereas those prepared from the serum of a normal volunteer did not affect enzyme activity. As determined by the diazobenzyloxymethyl-filter technique, the relative concentration of antibodies in the sera of an individual with leukemia (in remission) increased severalfold during a relapse. These data suggest that the presence of antibodies to poly(A) polymerase may be characteristic of sera from cancer patients and that the relative concentration of these antibodies may be indicative of the disease state. (Author abstract) (26 Refs)

33. ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY IN HUMAN CANCER: CHARACTERIZATION OF PATIENT LEUKOCYTE ACTIVITY AND TREATMENT EFFECTS.

Hersh EM, Murphy SG, Gutterman JU, Morgan J, Quesada J, Zander A, Stewart D
M. D. Anderson Hosp. and Tumor Inst., 6723 Bertner Ave., Houston, TX, 77030
Cancer; 49(2):251-260 1982

Antibody-dependent cell-mediated cytotoxicity (ADCC), mediated by peripheral blood Hypaque-Ficoll separated mononuclear cells, was studied in humans using chicken erythrocytes (CRBC) incubated in a 1:1,200 dilution of rabbit anti-CRBC and human B erythrocytes (HRBC) incubated in a 1:20 dilution of isoantibody. At the optimal target effector ratio of 3:1, ADCC to both CRBC and HRBC was significantly higher than normal in 27 lung cancer, 18 malignant melanoma, and 7 colon cancer patients, but not in 20 breast cancer patients. Chemotherapy (single-agent or combination) in 12 patients did not affect ADCC in vitro but significantly suppressed ADCC to both targets after only 4 or 5 days of therapy in vivo (ADCC to CRBC, 47.4 to 24.1% lysis: ADCC to HRBC, 48.1 to 16.3% lysis). Immunotherapy with intravenous (IV) Corynebacterium parvum or IV methanol extraction residue of BCG (MER) boosted ADCC to both targets within 4 to 7 days of the first dose. It was found that ADCC to HRBC but not to CRBC was completely absent in three cases of active hairy cell leukemia but was present in two cases in remission. The ADCC to HRBC showed an age-dependent increase in both the 51 normal subject and the cancer patients. This was not observed for ADCC to CRBC. The ADCC to CRBC was mediated mainly by an Fc-receptor-positive, nonadherent, small lymphocyte, and ADCC to HRBC was mediated entirely by an adherent monocyte. The ADCC did not correlate significantly with the H3 thymidine incorporation of peripheral blood mononuclear cells, cultured without stimulation for either 1 or 7 days. It also did not correlate with the number of residual granulocytes in the mononuclear cell suspensions. Measurement of ADCC is a useful method of characterizing host defense in malignant disease and its modification by therapy. (Author abstract) (48 Refs)

34. MAXIMIZING DIFFERENCES IN THE CONCANAVALIN A-INDUCED BLASTOGENIC RESPONSES OF LYMPHOCYTES FROM BREAST CANCER PATIENTS AND CONTROLS BY THE USE OF ALPHA-METHYL-D-MANNOSIDE.

Distasio JA, Cheresh DA, Schilder RJ, Vogel CL, Silverman MA, Lopez DM
Dept. Microbiology D4-4, Univ. Miami Sch. Medicine, P.O. Box 016960, Miami, FL, 33101
JNCI; 68(1):69-74 1982

In an attempt to magnify differences in the immune responses of potentially immunosuppressed cancer patients and normal controls, an assessment was made on the effects of the competitive inhibitor alpha-methyl-D-mannoside on the concanavalin A (Con A)-induced blastogenic responses of lymphocytes from each of these populations. Lymphocytes from breast cancer patients with metastatic disease were significantly deficient in their capability to undergo blast transformation regardless of whether the monosaccharide inhibitor was added to the assay cultures. In contrast, lymphocytes from breast cancer patients who did not display metastatic disease were capable of normal blastogenic responses to Con A. The addition of alpha-methyl-D-mannoside to lymphocyte cultures caused a significantly greater inhibition of the blastogenic responses of these patients' cells as compared to cells of normal controls. Thus the monosaccharide seems to serve as a useful reagent for optimizing differences between lymphocyte blastogenic responses of normal donors and those of immunodepressed donors. The results suggest that lymphocytes from breast cancer patients without clinically evident metastases possess some modification of their cell membrane. One possibility discussed was that the number or distribution of receptors for Con A on the membrane of lymphocytes of these patients is deficient. (Author abstract) (27 Refs)

35. GENERATION OF MONOCLONAL ANTIBODIES REACTING WITH HUMAN NORMAL AND NEOPLASTIC MAMMARY DUCT EPITHELIAL CELLS (MEETING ABSTRACT).

Menard S, Colnaghi MI, Tagliabue E, Canevari S, Fossati G, Sonnino S
Istituto Nazionale Tumori, Milano, Italy
Hybridomas and Cellular Immortality (Second Houston Symposium), November 5-6, 1981, Houston, Texas. University of Texas Medical School at Houston, 55 pp., 1981.

A monoclonal antibody was obtained from a hybridoma line generated by the fusion of P3 myeloma cells with spleen cells of a mouse immunized with cell membrane extracts from the human breast cancer cell line MCF-7. The specificity was studied by isotopic immunoglobulin assay on several cell lines and cell membrane extracts from various surgical specimens and milk cells; by membrane immunofluorescence on cell lines and cell suspensions obtained from fresh tumors; by immunofluorescence and immunoperoxidase technique on histological slices from about 100 different normal or neoplastic tissues. The structure recognized by the monoclonal antibody was found on normal epithelial cells of mammary duct and on 80% of the 50 breast carcinomas tested. The antigenic activity was unaffected by treatment with trypsin, Vibrio cholerae neuraminidase and by heating the cells at 100C but was inactivated by treatment with methanol. When lipid extracts for MCF-7 membrane preparations were chromatographed on diethylaminoethyl cellulose Sephadex the antigenic activity was recovered only on the neutral ganglioside fraction. (no Refs)

36. ANTIGENS ON NATURALLY OCCURRING ANIMAL AND HUMAN TUMORS DETECTED BY MONOCLONAL ANTIBODIES.

Embleton MJ, Gunn B, Byers VS, Baldwin RW, Bonavida B, Martin WJ, Ferrone S
Cancer Res. Campaign Lab., Univ. Nottingham, Nottingham, NG7.2RD, England
Transplant Proc; 13(4):1966-1969 1981

Reactivities of monoclonal antibodies prepared against a spontaneously arising rat mammary carcinoma and human osteogenic sarcoma cells were studied. An antibody-secreting hybridoma was prepared by fusion of the mouse myeloma P3-NS1-Ag4 (P3NS1) with spleen cells from rats immunized against a syngeneic mammary carcinoma, Sp4. The monoclonal antibody produced reacted only with mammary carcinoma Sp4 and did not bind to other rat tumors or normal rat cells. Two cell lines (791T/36 and 791T/48) from hybridomas obtained by the fusion of spleen cells from BALB/c mice immunized with the 791T osteogenic sarcoma cell line with P3NS1 cells, produced antibody that reacted preferentially with 791T cells. Antibody 791T/36 reacted strongly with 791T cells and with another osteogenic sarcoma, 788T, and more weakly with two others, 805T and 845T; the antibody did not react with six other osteogenic sarcomas. Tests against 11 lines of cultured fibroblasts, including 3 lines derived from the donor of 791T and 2 from donors of cross-reactive sarcomas, were negative. Monoclonal antibody from 791T/48 gave different cross-reactions. Two different monoclonal antibodies to a human osteogenic sarcoma cell line reacted with the immunizing cell line but not with cultured fibroblasts from the tumor host. Neither showed specificities for blood group or D-locus antigens. Despite apparent tumor association, the antigens detected by the monoclonal antibodies were not shared by all osteogenic sarcomas and were not restricted to this tumor type. (10 Refs)

37. AGE- AND SEX-RELATED DIFFERENCES IN ANTIBODY FORMATION AND BLASTOGENIC RESPONSIVENESS OF SPLENOCYTES FROM RIII MICE DEVELOPING VIRUS-INDUCED MAMMARY ADENOCARCINOMA.

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Dept. Medical Microbiology and Immunology, Univ. South Florida Coll. Medicine, Box 10, 12901 North 30th St., Tampa, FL, 33612
JNCI; 67(6):1347-1351 1981

Inbred RIII mice, known to be infected neonatally with murine mammary tumor virus so that females develop mammary adenocarcinoma by 12-15 mo of age, were examined with regard to antisheep red blood cell antibody responses at the cellular level. Female mice, 3-11 mo old, compared to male mice of the same ages had consistent and significant depression of the antibody response of their splenocytes. Furthermore, female mice with adenocarcinoma showed an even greater depression of the antibody response. Spleen sizes were consistently increased in females as compared to those of male mice throughout the first yr of life. The blastogenic responsiveness of the splenocytes to the B-cell mitogen Escherichia coli lipopolysaccharide and the T-cell mitogen phytohemagglutinin-P was not significantly different between male and female mice during the same periods, although the responses of the older tumor-bearing female mice to phytohemagglutinin-P were lower than those of non-tumor-bearing female mice. A complex relationship between age, sex, and immune responsiveness was evident in these mammary tumor virus-infected mice, which made it difficult to attribute a specific immune event to emergence of the mammary adenocarcinomas in the female as compared to male mice. (Author abstract) (9 Refs)

38. INTRACELLULAR STORAGE OF IGA AND SECRETORY COMPONENT IN CARCINOMAS OF THE FEMALE BREAST.

Syre G, Sehn M
Institut fur Pathologische Anatomie der Universitat Wien, Spitalgasse 4, A-1090 Wien, Austria
Virchows Arch [Pathol Anat]; 393(3):315-320 1981

This study reports 10 cases of mammary carcinoma with intracytoplasmic lumina and inclusion bodies visible by light microscopy; five tumors were classified as lobular in type and four as different forms of infiltrating ductular carcinomas. One tumor showed a lobular growth in combination with ductular structures. For the identification of the inclusion bodies, indirect immunofluorescence on paraffin embedded material was performed, which revealed IgA as well as secretory component within the intracytoplasmic lumina. It was concluded that the production of secretory component and the uptake of IgA is possible even in carcinomas without glandular structures, and that immunomorphology should supplement histological and histochemical evaluation in order to define the contents of intracytoplasmic lumina. (Author abstract) (21 Refs)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

39. MAMMARY TUMOR VIRUS DNA CONTAINS SEQUENCES REQUIRED FOR ITS HORMONE-REGULATED TRANSCRIPTION.

Ucker DS, Ross SR, Yamamoto KR
Dept. Biochemistry and Biophysics, Univ. California, San Francisco, San Francisco, CA, 94143
Cell; 27(2):257-266 1981

Glucocorticoids regulate the rate of transcription of integrated murine mammary tumor virus (MTV) genes in most clones of MTV-infected rat hepatoma tissue culture (HTC) cells. To determine whether hormonal regulation is mediated from flanking cellular sequences or rather from within the viral DNA, we analyzed the relative rates of transcription of MTV and adjacent HTC sequences in two lines of infected HTC cells, J2.15 and J2.17, each of which contains a single insertion of MTV DNA. In addition, we measured in uninfected HTC cells the transcriptional rates of the corresponding 'preinsertion fragments,' which may be viewed as the equivalent sequences bearing deletions of MTV DNA; the two genomic segments into which integration occurred in the two lines are unrelated. Previous work showed that glucocorticoids induce the accumulation of MTV RNA in J2.17, whereas viral transcripts are not detected in J2.15. RNA pulse-labeling experiments indicate that glucocorticoids stimulate the rate of MTV gene transcription in J2.17 but not in J2.15; in contrast, no labeled RNA hybridizing to flanking sequences was detected either in the uninfected or in the infected cells. We conclude that the host site of integration of MTV need not be transcriptionally active or hormonally responsive to permit viral gene expression. Furthermore, these rate measurements indicate that glucocorticoid-stimulated MTV RNA synthesis in J2.17 does not reflect readthrough transcription from a regulated cellular promoter. This notion is independently supported by transcript mapping experiments showing that the 5' terminus of nuclear MTV RNA is at a site on MTV DNA approx 1.2 kb downstream from the host-viral junction. Thus our data are consistent with the presence of a hormone-responsive element within the provirus. (Author abstract) (32 Refs)

40. DEXAMETHASONE INDUCTION OF THE INTRACELLULAR RNAS OF MOUSE MAMMARY TUMOR VIRUS.

Robertson DL, Varmus HE
Graduate Section Biochemistry, Dept. Chemistry, Brigham Young Univ., Provo, UT, 84602
J Virol; 40(3):673-682 1981

We have studied the kinetics of dexamethasone induction of mouse mammary tumor virus (MMTV) RNAs and proteins in virus-infected rat XC cells and GR mouse mammary tumor cells. A detectable increase in viral RNA in infected XC cells was present within 10 min after hormone addition, and half-maximal induction was achieved in less than 2 hr. The increase in viral RNA concentration was apparent first in nuclear RNA and later in the cytoplasm. Within the first 15 min of induction, only genome-sized RNA (35S, 7.8 kilobases) was present in augmented amounts, whereas the major subgenomic RNA (24S, 3,8 kilobases) did not appear until at least 30 to 60 min postinduction. The sequential appearance of these RNAs, the probable mRNA's for the gag and env proteins, paralleled the order of appearance of the gag and env proteins, respectively, after hormone treatment. An additional species of viral RNA (20S, 2.5 kilobases) was detected during these induction experiments, but the role of this RNA is not known. Both subgenomic RNAs contain sequences derived from both the 5' and 3' termini of genomic RNA and are presumably spliced. After dexamethasone induction of infected XC cells, we detected two smaller env-related proteins which were not found in full hormone induction. The functional role of these smaller proteins is not known. A previously reported smaller species of RNA (13S, 1.0 kilobase) did not appear to be induced and was shown to be cellular rather than viral in origin. In the fully induced infected XC and GR mammary tumor cells, the only viral RNAs present were the 35S and 24S RNAs. In addition, mammary tumors contained only these two viral RNAs. Thus, tumor cells appear to contain only the viral RNAs which direct the synthesis of the gag, pol, and env proteins of the virion. (Author abstract) (43 Refs)

41. GENETIC MAPPING OF ENDOGENOUS MOUSE MAMMARY TUMOR VIRUSES: LOCUS CHARACTERIZATION, SEGREGATION, AND CHROMOSOMAL DISTRIBUTION.

Traina VL, Taylor BA, Cohen JC

Dept. Microbiology and Immunology, Tulane Medical Center, New Orleans, LA, 70112

J Virol; 40(3):735-744 1981

The restriction endonuclease EcoRI has been used to study the inheritance of strain differences in endogenous mouse mammary tumor virus DNA sequences. This enzyme, which cleaves at only one site within the nondefective viral genome, generates DNA fragments containing mouse mammary tumor virus sequences which vary in size according to the locations of EcoRI restriction sites in the flanking mouse sequences, thereby defining unique integration sites of the viral genome. Recombinant inbred strains of mice have been used to study the inheritance of these DNA fragments which hybridize to mouse mammary tumor virus cDNA sequences. The results define 11 segregating units consisting of one or two fragments. These units were shown to segregate among the recombinant inbred strains, and in some instances linkage was established. Two units were shown to be linked on chromosome 1. Another unit was mapped to chromosome 7, which is presumably identical to the previously defined genetic locus Mtv-1. One other mouse mammary tumor virus locus was tentatively assigned to chromosome 6. The results are consistent with the view that integration of mouse mammary tumor virus can take place at numerous sites within the genome, and once inserted, these proviruses appear to be relatively stable genetic entities. (Author abstract) (45 Refs)

42. ORIGIN OF A MALIGNANT ADENOCARCINOMA CELL LINE INDUCED BY RETROVIRUS-LIKE PARTICLES FROM DMBA RAT MAMMARY TUMORS.

Holzel F, Sakuma S, Hanke D

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J Cancer Res Clin Oncol; 102(1):31-42 1981

Intraperitoneal inoculation of neonate Sprague Dawley rats with cell-free extracts containing retrovirus-like particles from DMBA-induced rat mammary tumors resulted in a fivefold increase of benign mammary neoplasias in the survivor animals, in comparison to the spontaneous tumor incidence rate. In addition, four animals developed metastasizing abdominal adenocarcinomas. The ascitic cells of one of the abdominal tumors were established as a permanent tissue culture line (HH-1). After subsequent animal passage, cells of the permanent line HH-9 clone 14 showed increased malignancy manifested by the number of takes per animals injected, and by the number of remote metastases observed. (Author abstract) (26 Refs)

RADIOLOGICAL ASPECTS OF MAMMARY GLAND CARCINOGENESIS

43. THE ATOMIC BOMB SURVIVORS AND THE PROBLEM OF LOW-DOSE RADIATION EFFECTS.

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Am J Epidemiol; 114(6):761-783 1981

The effects of low-dose radiation (0.1 to several rads/yr continuously or up to 10-20 rads in a single dose) are discussed in relation to data accumulated on atomic bomb survivors (ABS). Although ABS provide the largest available resource for human studies on the genetic effects of ionizing radiation, their number is not large enough to give direct information on effects in the low-dose region; a dose-response relationship does seem to exist for both Hiroshima and Nagasaki ABS. The relationship between radiation and disturbances in growth and development, somatic cell chromosomal aberrations, and carcinogenesis are discussed. Dose-response models are considered in relation to leukemia in ABS. Even with 550 cases observed in ABS between 1946 and 1974, determination of the real low-dose risk has not been possible. Using ABS data, a linear model appears suitable for the description of breast cancer incidence following low-dose radiation. Data from ABS survivors provide little information on the incidence of thyroid cancer following low-dose radiation from ABS. The relationship between low-dose, low linear energy transfer and other cancers observed in ABS is discussed. (60 Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

44. MAINTENANCE OF PROLACTIN RECEPTORS IN HUMAN BREAST CANCER.

Ben-David M, Dror Y, Biran S

Dept. Pharmacology, Hebrew Univ.-Hadassah Medical Sch., POB 1172, 91010 Jerusalem, Israel

Isr J Med Sci; 17(9/10):965-969 1981

Breast tissue specimens of 110 women with various stages of breast cancer were tested in vitro to determine their specific binding sites for human prolactin. In contrast to the case of steroid receptors, binding sites for prolactin were found in the vast majority of breast cancer tissue. Distribution profiles giving amount of prolactin receptor and their affinity coefficients were found to be similar in the tissues of women whose ages, hormonal status, or stage of breast cancer varied. These findings show that in contrast to steroid receptors, human breast cancer tissue maintains binding sites for prolactin. The findings also indicate that there may be a higher dependency of breast cancer on prolactin than on steroids. Clinical trials must be carried out to determine the role of 'positive' prolactin receptors in prognosis and prediction of response to future hormone therapy. (Author abstract) (20 Refs)

45. RELATIONSHIP OF GLYCOPROTEINS IN HUMAN BREAST CYSTIC DISEASE FLUID TO BREAST CARCINOMA (MEETING ABSTRACT).

Haagensen DE, Kister SJ, Dilley WG, Wells SA

Department of Surgery, Harvard Medical School, Boston, MA

International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Biochemical analysis of Human Breast Gross Cystic Disease Fluid has identified four major component proteins which are uniformly present. These four proteins have been termed Gross Cystic Disease Fluid Proteins (GCDFP) and were defined relative to their monomer mol size as GCDFP-70,44,24, and 15 (70,000, 44,000, 24,000, 15,000 Daltons). The GCDFP-24 and-15 account for over 70% of the total cyst fluid protein content. The GCDFP-70,-44, and-24 have plasma analogues by immunological analysis, however the GCDFP-15 is present in normal plasma only at very low levels (Av 28ng/ml). A radioimmunoassay for the GCDFP-15 has been utilized to measure levels of this molecule in various tissues and fluids. The normal body tissues which contain the GCDFP-15 (axillary sweat glands, perianal sweat glands, salivary glands) all have, in common, apocrine glandular features. The origin of breast gross cystic disease also appears due to apocrine metaplastic cells in the breast. Breast carcinoma tissues were found to have a 4 log range of GCDFP-15 content (10 to 10 ,000 ng/mg cytosol protein) with cribriform and comedointraductal carcinomas having the highest content. Analysis of plasma samples from patients with breast carcinoma has revealed that approx 40% of patients during the course of metastatic disease will develop significant plasma elevations of GCDFP-15 (range 150 to 74,000 ng/ml). The direction of change in serial plasma levels reflected alterations in the clinical course of metastatic disease with therapy. Of significant interest has been the finding that androgen treatment (Halotestin) can specifically stimulate carcinoma cell production of GCDFP-15. (no Refs)

46. HISTOCHEMICAL DETECTION OF STEROID BINDING PROTEINS IN BREAST CANCER TISSUE (MEETING ABSTRACT).

Hogel B, Jawny J, Eiermann W

University of Munchen, Munchen, W. Germany

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer, 131 pp., 1981.

Fifty tissue specimens of breast cancer routinely examined for hormone receptors by dextran coated charcoal assay were histochemically reexamined after storage in liquid nitrogen. HE-staining of cryostat sections yielded similar quality than those in fresh cryostat frozen sections. According to LEE the sections were treated after preincubation with 2% bovine serum albumin with either 17beta-estradiol-6-carboxy-methyl oxime-bovine serum albumin-fluorescein isothiocyanate (FLUORO-CEPTM) or 11alpha-hydroxyprogesterone hemisuccinate-bovine serum albumin-tetramethylrhodamine isothiocyanate (FLUORO-CEPTM). After washing out the unbound conjugate the sections were examined with a fluorescent microscope equipped with appropriate filters for fluorescein and rhodamine exitations. Unspecific binding could be neglected as shown by several controls. There was a good correlation concerning results of estrogen receptor (ER) and progesterone receptor (PgR) negative tumors in both biochemical assay (BA) and histochemical assay (HA). Positive results for ER and PgR were obtained as well in HA, BA or HA/BA. (no Refs)

47. ESTROGEN AND PROGESTERONE RECEPTORS IN INTRADUCTAL BREAST CARCINOMAS (MEETING ABSTRACT).

Mignot L, Pichon MF, De Roquanncourt A, Naiditch M, Marty M, Gorins A

No affiliation given

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Hormonal receptors status is relatively unknown in intraductal breast carcinoma (CGIS). Fourteen patients with tumoral CGIS were studied, 7 with pure in situ ductal carcinomas and 7 predominantly intraductal with less than 10% stromal infiltration (10 premenopausal patients: median age 43 yr, 4 postmenopausal median 53 yr). Cytosolic estrogen (ER) was studied in 14 patients and cytosolic progesterone (PR) in 10 patients. ER+ (greater than 10 fmol/mg protein) was present in 9/14 patients (65%) with 20 +/- 24 fmol/mg protein mean range, PR + was present in 8/10 patients with 40 +/-43 fmol/mg protein mean range. These results were compared with those observed in 70 pure infiltrative breast carcinomas: ER + equals 46/70 patients (65%) with 70 +/-39 fmol/mg mean range and PR + equals 40/70 patients (57%) with 103 +/- fmol/mg mean range. ER and PR positive rate were identical for the two histopathological groups. However mean value, total median and positive rates median value were statistically lower in intraductal carcinomas than in infiltrative carcinomas, for both ER and PR receptors (Kolmogoroff Smirnoff test p less than 0.005). Histopathological hypothesis such as the influence of lymphoid infiltration will be discussed and results compared with observations in literature. (no Refs)

48. NON-RECEPTOR PROGESTERONE-ESTROGEN BINDING PROTEIN IN HUMAN MAMMARY CARCINOMA (MEETING ABSTRACT).

Mossler JA, Levine SE, Woodard BH, Brown ML, McCarty KS

Department of Pathology, Duke University Medical Center, Durham, NC, 27710

Am J Clin Pathol; 76(3):352 1981

Estrogen receptor assay improves selection of patients with metastatic mammary carcinoma for hormone therapy. We have examined the sensitivity, specificity, and predictive value of estrogen and progesterone receptors utilizing multiconcentration saturation analyses (DCCA) and more laborious and expensive sucrose density gradient analyses (SDGA). The specificity and predictive value of the SDGA is greater than that of DCCA. The presence of an intermediate affinity 4S steroid binding protein with specific decay characteristics (PEBP) may well explain the loss of sensitivity and specificity of the titration analyses. DCCA fails to separate this PEBP from specific 8S receptor proteins. The PEBP is not cortisol binding globulin or testosterone-estrogen binding globulin. The quantity of PEBP correlates with the number of apocrine type granules identified by electron microscopy in the cytoplasm of mammary carcinoma cells. This protein may represent a significant source of interference with assays for specific steroid receptor when gradient techniques are not utilized. (no Refs)

49. AFFINITY CYTOCHEMISTRY VISUALIZES SPECIFIC ESTROGEN BINDING SITES ON THE PLASMA MEMBRANE OF BREAST CANCER CELLS.

Nenci I, Marchetti E, Marzola A, Fabris G
Istituto di Anatomia e Istologia Patologica, Univ. Ferrara, 44100 Ferrara, Italy
J Steroid Biochem; 14(11):1139-1146 1981

A cytochemical technique involving estradiol labeled covalently with macromolecular fluorescent probes was used to detect possible estrogen-binding sites on the plasma membrane of viable human breast cancer cells. At 4 C, breast cancer cells, but not other non-epithelial cell types, showed bright fluorescence diffusely distributed over the cell surface and in a ring pattern. Binding occurred by a saturable pathway, because pretreatment of cells with the same ligand in 'cold' form abolished labeling. Non-estrogen steroid hormones; synthetic estrogen, and anti-estrogen did not hinder binding, indicating that binding is structurally specific for natural estrogen. Binding sites showed temperature-sensitive lateral mobility in the plane of the membrane, which led to formation of small clusters, patches, and polar caps at 23 or 37 C. Results indicate that estrogen-target cells have plasmalemmal estrogen-binding sites, which do not involve classical cytoplasmic receptors. Translational mobility of binding sites is consistent with their potential receptor nature. (40 Refs)

50. UNOCCUPIED BINDING SITES FOR OESTROGEN IN NUCLEI OF A BREAST TUMOR CELL LINE (MCF-7).

Geier A, Haimsohn M, Malik Z, Lunenfeld B
Inst. Endocrinology, Chaim Sheba Medical Center, Tel Hashomer, Israel
Biochem J; 200(3):515-520 1981

A method to measure both occupied and unoccupied estrogen receptors directly in the crude nuclear fraction of the MCF-7 cells was developed. The receptors had high affinity for estradiol (Kd approx 0.7 nm) and binding specificity characteristics of estrogen receptors. A substantial amount of the unoccupied receptors were found in the crude nuclear fraction. Several experiments excluded the possibility that the unoccupied nuclear receptor might be a cytoplasmic contaminant. Multiple extractions with Tris buffer released about 75% of the total receptor content, leaving the rest unextractable in the crude nuclear fraction. Nuclei purified by centrifugation through 1.8 M-sucrose and treatment with 0.7% Triton X-100, or by centrifugation through 50% glycerol with 0.1% Triton X-100 contained similar amounts of unoccupied receptors to that found in the crude nuclear fraction. In cells cultured during 5 days after preconfluency a three-fold increase in the amount of unoccupied cytoplasmic receptors occurred, whereas the amount of unoccupied nuclear receptors did not change significantly and conversely in cells exposed to increasing concentrations of estradiol the unoccupied cytoplasmic receptor was continuously depleted but no considerable change in the unoccupied nuclear receptor was found. (Author abstract) (23 Refs)

51. THE PRESENCE OF A SECOND, SPECIFIC ESTROGEN BINDING SITE IN HUMAN BREAST CANCER.

Panko WB, Watson CS, Clark JH
Dept. Pathology, Baylor Coll. Medicine, Houston, TX, 77030
J Steroid Biochem; 14(12):1311-1316 1981

Type II estrogen binding site (II EBS) was analyzed in human breast tumor specimens. Saturation analysis of cytosol derived from pooled tumor specimens was conducted over the 3H-estradiol (3H-ES) concentration range 0.5-120 nanoM (nM). Scatchard plotting of saturation data revealed the presence of a two-component binding system. The type I site, believed to be cytoplasmic estrogen receptor (ER), displayed an affinity and concentration compatible with the ER system. The type II site had a markedly lower affinity for 3H-ES and significantly higher concentration. A similar two-component Scatchard plot was obtained when moxestrol was used with a different pool of tumor tissue. The post-labeled sucrose gradient method was used with cytosol derived from pooled tumor tissue. If cytosol was pre-labeled with 40 nM 3H-ES, the specific binding at both the 8S and 4S regions of the gradient showed some augmentation. However, if the cytosol was post-labeled, marked augmentation of specific binding in the 4S region of the gradient occurred. Tumors of the colon (2), lung (2), and muscle (1) were subjected to pre- and post-labeled sucrose gradient analysis with 40 nM 3H-ES. The difference between specific binding in the 4S region of the pre-labeled (2 nM) and the post-labeled (40 nM) gradient was defined as the amount of type II EBS in the tumor. Neither ER nor type II EBS were detected in any of the five tumors. When the concentration of type II EBS was correlated with the concentration of ER, a very strong positive correlation was noted. The results indicated that breast cancer cytosol contains a specific, secondary estrogen binding site. (16 Refs)

52. USE OF FLUORESCENT PROBES FOR ANALYSES OF STEROID RECEPTORS (MEETING ABSTRACT).

Kute TE, Crumb K, Miller B, Barrows G
Bowman Gray School of Medicine, Winston-Salem, NC
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

Steroid receptor analysis has been shown to be useful in the prediction of response of hormone therapy in breast cancer patients. However, the assay is tedious and gives results of a general nature, ie, femtomoles per mg of cytosol protein. Our lab has been working on a new method of analysis using flow cytometry. Using the method of Muller and Wotiz, we prepared a viable cell suspension from immature rat uterine tissue as determined by fluorescein diacetate analysis and flow cytometry. Scatchard analysis of this cell suspension demonstrated a specific uptake 152 femtomoles of 3H-estradiol (3H-E2) per 1 x 10(6) cells with an affinity constant of 2.4 x 109M-1. Correction for non specific uptake was determined by adding 100 fold excess of estradiol to 3H-E2 cell suspension reactions. Sucrose density gradients analysis of the cytoplasmic extract indicated the presence of an 8S and 4S estrogen receptor in this cell suspension. A fluorescent labeled estrogen was prepared by Barrows et al and found to compete with 3H-E2 for the steroid receptor. However, this product was shown to be contaminated with estradiol by thin layer chromatography and high pressure liquid chromatography. Coumestrol, a fluorescent estrogen, was therefore used since it can be obtained in large quantities and has a relative affinity constant of 6 x 108M-1 determined by competition studies. Experiments using flow cytometry and this fluorescent probe indicate no specific uptake in the immature rat uterine cell suspension, two breast cell lines or neutrophiles. There was, however, non specific fluorescent uptake observable by flow cytometry and fluorescent microscopy. This fluorescence intensity was a function of the coumestrol added (10(-5) to 10-8M) and this cell fluorescent intensity was reduced by washing the cell preparations. Future work in this area will be discussed. (2 Refs)

53. STUDIES TO DETECT ESTROGEN RECEPTORS IN INTACT CELLS USING CYTOFLUOROMETRIC TECHNIQUES (MEETING ABSTRACT).

Tyrer HW, Fipho CJ, Mitra A, Oxenhandler R
Cancer Research Center, University of Missouri, Columbia, MO
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire Memorial Sloan-Kettering Cancer Center; 1981

We are developing assays to quantitate estrogen receptors in intact cells using a fluorescienated 17 beta-estradiol (17-FE). Although there is substantial physiologic and biochemical interest in studying estrogen binding reactions, 50-60% of mammary tumors with specific estrogen receptors respond to endocrine manipulations, whereas estrogen receptor negative tumors generally do not respond. Estrogen receptor studies using 3H-17-beta-estradiol and 17-FE have been performed in intact cells and cytosol of: 1) An estrogen receptor positive cell line derived from a rat pituitary tumor (GH3), 2) Estrogen negative cell line also derived from a rat pituitary tumor (RP2), and 3) Clinical samples obtained from the Ellis Fischel State Cancer Hospital. The 17-FE inhibits 17-beta-estradiol binding nearly as well as Diethyl stilbesterol, which is used for direct specific binding. Flow cytometry data follows the radiometric data. Cells from GH3 line show positive differences between total receptor fluorescence distribution and the non-specific receptor fluorescence distribution, whereas the RP2 lines show no differences. The differences between the distribution from GP3 cell lines correspond to about 60,000 receptors per cell. (no Refs)

54. COMPARISON OF STEROID RECEPTOR CONTENT AND DNA LEVELS IN HUMAN BREAST CANCERS (MEETING ABSTRACT).

Thornthwaite JT, Coulson PB
Departments of Biophysics and Physiology, Quillen-Dishner College of Medicine, East Tennessee State University, Johnson City, TN, 37614
VIII Conference on Analytical Cytology and Cytometry, May 19-25, 1981, Wentworth-by-the-Sea, New Hampshire, Memorial Sloan-Kettering Cancer Center; 1981

The purpose of this study was to determine if there is any correlation between the degree of heteroploidy in human breast cancers and the quantity of steroid receptors in these tissues. Fro zen specimens (-85 C) with estrogen cytosolic receptor levels between 0-502 fm/mg cytosolic protein were prepared for DNA flow cytometric analysis. This was accomplished by mincing the tissues in a special nuclear isolation medium (NIM) containing 10 ug/ml of 4',6-diamindino-2 phenylindole-2HCl (DAPI) at room temperature. The isolated nuclei were filtered (70 micron mesh) and syringed to assure a monodispersed nuclear population. A modified PHYWE ICP-21 flow cytometer, either with the PHYWE flow chamber for DNA or the Cell Technology transducer for dual parameter analysis (electronic nuclear vol vs DNA fluorescence) was utilized. The range of CVs of the G1/0 peaks of NIM-DAPI prepared tissues were routinely 1-3%. Samples were grouped according to their DNA contents and designated diploid-like, diploid/hypodiploid, diploid/hyperdiploid, diploid/multiploid, or diploid/hypertetraploid. No correlation could be seen between the percentage of hyperdiploid cells or the proliferation index compared to the estrogen (3H-estradiol), progesteron (3H-R5020) or, testosterone (3H-R1881) receptor levels. In 84 tumors, the percentage of breast cancers which were diploid or aneuploid were 30% or 70%, respectively. Work is in progress to see if there is any correlation between the degree of aneuploidy and recurrence. (no Refs)

55. HISTOCHEMICAL DEMONSTRATION OF ESTROGEN RECEPTORS IN BREAST CANCER.

Paulsen SM, Johansen P, Rasmussen KS, Mygind H
Patologisk institut, Aalborg sygehus Nord, DK-9000 Aalborg, Denmark
Ugeskr Laeger; 143(47):3119-3123 1981

Histochemical method for the detection of estrogen receptors (ERs) in breast carcinoma tissue is described, and results obtained by this method in tissue specimens from 46 breast cancer patients are reported. The histochemical detection of ERs is based on counting of fluorescent (positive) cells after incubation with fluorescein isothiocyanate-conjugated 17-beta-estradiol. ER+ carcinomas were defined as those containing more than 10% fluorescent cells, which was found consistent with the biochemical criterion of ER+ breast carcinoma (greater than 10 femtomoles/mg protein). The patients included 14 premenopausal and climacteric patients (Group I) and 32 patients in the menopause (Group II). The frequencies of ER+ carcinomas were 8/14 in Group I and 24/32 in Group II. The frequencies of ER+ carcinomas were 25/38 for infiltrating ductal carcinomas, 6/7 for infiltrating lobular carcinomas, and 1/1 for colloid carcinoma. Even though the relationship between the histochemically and biochemically demonstrated ERs is not fully elucidated, the histochemical method is able to supplement the biochemical method. (15 Refs) (In DAN)

56. STEROID RECEPTORS IN A GROUP OF BRAZILIAN BREAST CANCER PATIENTS.

Brentani MM, Nagai MA, Fujiyama CT, Goes JC
Laboratorio de Oncologia Experimental Faculdade de Medicina, Universidale de Sao Paulo, Av. Dr. Arnaldo, 455-CEP, 02646 Sao Paulo, Brazil
J Surg Oncol; 18(4):431-439 1981

Two hundred and forty-two primary breast cancers were assayed for estrogen receptors (ER). Of these, 202 were analyzed for progesterone receptors (PR) and 155 for glucocorticoid receptors (GR). ER was positive in 58% of the specimens; PR and GR were positive in 57%. A positive association was found between ER but not PR or GR frequency and age. Frequency of ER, PR, and GR positivity was approx the same in premenopausal and postmenopausal women but ER content was much higher in postmenopausal women. About 70% of ER+ patients were also PR+ and GR+. Both frequency of PR positivity as well as av concentration, and frequency of GR positivity as well as av concentration were positively correlated with ER. (Author abstract) (30 Refs)

57. HORMONE RECEPTORS IN BREAST CANCER.

Fortuny IE, Bates HA
(c/o Bates) Res. Lab., Metropolitan Medical Center, 900 South 8th St., Minneapolis, MN, 55404
Minn Med; 64(12):761-763 1981

Standardization, quality control, and results of the hormone receptor assay are discussed. Primary breast cancer specimens were assayed for estrogen (ER), and/or progesterone (PR) hormone receptors. A total of 632/987 (64%) tumors tested were positive. The menopausal state was identified in 374/632 patients. Histologic description of 229 specimens was: 190 ductal carcinoma, 22 comedocarcinomas, 12 medullary carcinomas, 5 lobular carcinomas, 2 adenocarcinomas. Results obtained disclosed ER positive receptor in 85/145 (58.5%) premenopausal and 147/204 (67.5%) in postmenopausal patients. PR receptors are determined only if ER is positive. For both ER and PR receptors in 180 premenopausal patients were studied showing 133 (73.8%) with both positive receptors. Positive receptors were found in 90/123 (74%) postmenopausal patients. The hormone receptor determinations in breast cancer are important in prognosis and management. Meticulous control of sample storage, handling, periodic double testing of materials, and sample assays are important. (9 Refs)

58. FLUORESCEINATED ESTRONE BINDING BY HUMAN AND MOUSE BREAST CANCER CELLS.

Fisher B, Gunduz N, Zheng S, Saffer EA
Univ. Pittsburgh, 914 Scaife Hall, 3550 Terrace St., Pittsburgh, PA, 15261
Cancer Res; 42(2):540-549 1982

A proportion of single, intact, viable cells derived from mouse and human breast cancers, when incubated with 17-fluoresceinated estrone, displayed fluorescence in all instances. The percentage of cells which were marker positive in mouse mammary tumors was remarkably uniform (approx 35%), whereas in human breast cancers, it varied considerably (3 to 58%). While fluorescence of the entire cell most commonly occurred, staining of either the nucleus or the cytoplasm was observed frequently. Mouse uterus and liver were also marker positive. The proportion of such cells decreased in incidence following in vitro incubation with estradiol and tamoxifen or following administration of tamoxifen prior to tissue removal, findings indicative of 17-fluoresceinated estrone binding to estrogen receptor (ER). Experience with the cytochemical method as used in the present studies leads us to conclude that this is a technique which may by readily and rapidly carried out and is one which deserves more widespread evaluation. Since standard biochemical methods determine total ER in tumor cytosol and since cytochemical techniques measure the proportion of cells containing ER, the two are complimentary. When used simultaneously, they may provide more definitive information than is obtainable from either alone. (14 Refs)

59. SECRETION-ASSOCIATED LECTIN-BINDING SITES AS A PARAMETER OF HORMONE DEPENDENCE IN MAMMARY CARCINOMA.

Klein PJ, Vierbuchen M, Wurz H, Schulz KD, Newman RA
(c/o Newman) Membrane Immunology Lab., Imperial Cancer Res. Fund, Lincoln Inn Fields, London WC2A 3PX, England
Br J Cancer; 44(5):746-748 1981

Hormone dependency in mammary carcinoma was studied with the aid of lectins from peanut (PNA: peanut agglutinin) and Helix pomatia (HP), which have high affinities for D-galactosyl-(1-3)-N-acetyl-D-galactosamine and N-acetyl-D-galactosamine, respectively. Experiments were performed on formaldehyde-fixed tissue sections from 75 patients. After treatment of tissue sections with neuraminidase to expose any sialic acid-covered receptors, PNA binding was seen within cytoplasmic vacuoles of breast tissue with secretory malfunction; in well-differentiated carcinomas, binding to apical surfaces and on secretions lying within the glandular structures was observed. Of 46 specimens of mammary tumors, 68% had PNA receptors as well as estrogen (E) and progesterone (P) receptors. Only 45% had PNA receptors when only E receptors were detected. Only 23% of specimens with no detectable E or P receptors had PNA receptors. Greater PNA binding occurred in the primary tumors than in axillary-lymph node metastases. Responsiveness of 29 breast cancer patients to endocrine therapy was determined. Of lectin- (PNA and HP) positive patients, 82% showed a response to hormone therapy. Only 24% of the lectin-negative group showed similar responses. A poor correlation was found between lectin-receptor expression and response to chemotherapy. Results indicated that the lectin-binding method is a useful hormone-receptor assay. (7 Refs)

60. PEROXIDASE ACTIVITY AS A MARKER FOR ESTROGENICITY: STUDIES IN UTERUS AND MAMMARY TUMORS.

Levy J, Liel Y, Glick SM
Dept. Endocrinology, Soroka Medical Center, 84101 Beersheba, Israel
Isr J Med Sci; 17(9/10):970-975 1981

We examined the possibility that peroxidase activity might be a marker for estrogen activity in established estrogen-dependent tissues: dimethylbenz[a]anthracene (DMBA)-induced rat mammary tumors and human breast cancer. In DMBA-induced tumors undergoing regression after ovariectomy or tamoxifen treatment, tumor size decreased by 50%, estradiol receptors (ER) and progesterone receptors (PgR) decreased by 25 and 20%, respectively, but peroxidase activity paradoxically increased six- to sevenfold. In DMBA tumors stimulated by estradiol treatment or by the cessation of tamoxifen administration in intact rats, tumor size increased threefold. ER and PgR increased two- and threefold, respectively, while peroxidase activity decreased 50%. These data indicate an inverse relation between tumor growth, ER and PgR on the one hand, and peroxidase activity on the other. In the human breast cancers there was a significant negative relation between the presence of ER and peroxidase activity. By using a calibrated Sephadex G-100 column it was shown that uterine peroxidase differs in molecular weight from the peroxidase of rat mammary tumors and that of human breast cancer. (Author abstract) (21 Refs)

61. HISTOLOGY AND HISTOCHEMISTRY OF CYSTIC BREAST DISEASE (MEETING ABSTRACT).

Bussolati G, Papotti M, Gugliotta P
Istituto di Anatomia e Istologia Patologica, University of Turin, Torino, Italy
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

The various morphological aspects grouped under the term of cystic breast disease are the result of the multifactorial effects of different hormones on the two cell types (ie the secretory or epithelial and the myoepithelial cells) of the terminal intra-lobular ductules. Hyperplasia and metaplasia of the epithelial and/or the myoepithelial cells and cyst formation of various size are the main features of this disease. Whether a progression (grades 1 to 5) can be traced from simple hyperplasia to more atypical patterns, with a final development of 'in situ' and then invasive carcinoma can be discussed. Most pathologists, for theoretical and practical reasons, consider however benign cystic disease and carcinomas (either lobular or ductal) as separate entities. Their well known association does not 'per se' indicate a transition from one disease to the other, nor is such transition fully substantiated by histological evidences. Some features however, such as the 'gross cystic disease' seem to display a higher degree of association with breast cancer and deserve therefore more attention. The histogenesis of the various forms of cystic disease can be fruitfully investigated by means of histochemical methods to detect: a) mild proteins (such as casein, lactalbumin, lactoperoxidase, the Milk Fat Globule Membrane antigen and steroid receptors) in the epithelial (secretory) cells, or b) contractile proteins (actin, myosin) which can be regarded as markers of the myoepithelial cells. (no Refs)

62. MILK PROTEINS AND BREAST CANCER (MEETING ABSTRACT).

Zangerle FF, Collette J, Hendrick JC, Franchimont P

Radioimmunoassay Laboratory, Univesity of Liege, Liege, Belgium

International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Normal mammary gland function is expressed by synthesis of proteins. Among the milk proteins, alpha lactalbumin and gross cyst fluid disease protein 70 (GCDFP 70) are now assayed in our laboratory. The respective radioimmunoassays have been validated and applied on serum, breast secretion and organ breast culture medium. In serum, alpha lactalbumin in detected, with wider dispersion and higher values in women than in men. Lactalbumin appears to be an excellent index of breast activity as shown by its levels in sera of gestating or lactating women. The prolactin is significantly higher in the sera of women with lactalbumin than in the sera of women without lactalbumin. When lactalbumin is detectable, its values are cyclated during menstrual cycle with higher values during luteal phase. Lactalbumin in found with higher incidence in the serum of patients with breast cystic disease but not at all in the serum of breast cancer patients. GCDFP 70 is only found in sera of women with breast cyst disease and breast cancer but not in serum of patients with other carcinomas. Cyst fluid and breast secretion, alpha lactalbumin and GCDFP have been assayed in cyst fluid from patients with breast cystic disease and in breast secretion, from normal women, collected by nipple aspirates. The concentrations of GCDFP are very high (in the range of mg/ml) compared to those of lactalbumin (ng/ml) and in the same order. With these first results, there is no evidence of variation of GCDFP or lactalbumin concentrations in breast secretion according to the presence or absence of cancer in the aspirated breast. Culture medium, organ culture of breast cancer was carried out. Ninety per cent of the cancerous explants produce GCDFP 70 with levels the day 2 compared with those in day 1. In contrast, normal breast does not secrete any detectable amount of GCDFP in the same conditions. Lactalbumin is rarely secreted by breast carcinoma and normal breast tissue in culture. In breast cancer fluid, the levels of GCDFP are not related to: menopausal states of the patient, tumor estrogen receptors, whether the cancer tissue was derived from primary tumor or invaded node, from patient with early or late disease. (no Refs)

63. DIFFERENCES IN MICROCALCIFICATION IN BREAST TUMORS.

Busing CM, Keppler U, Menges V

Pathologisches Institut, Klinikum der Stadt Mannheim, Theodor-Kutzer-Ufer, D-680 0 Mannheim 1, W. Germany

Virchows Arch [Pathol Anat]; 393(3):307-313 1981

Microcalcifications in benign and malignant tumors can be analyzed by x-ray diffraction and electron microprobe analysis in human specimen. Our systematic investigations revealed calcium hydroxyapatite in cases of invasive carcinoma but calcium oxalate (weddelite) in proliferating but non-invasive diseases. The differences in calcification depending on the underlying disease may indicate basic differences in cell metabolism. (Author abstract) (10 Refs)

64. THE SYNTHESIS OF A PROTEINASE INHIBITOR, ALPHA-1-ANTICHYMOTRYPSIN, BY HUMAN BREAST EPITHELIAL CELLS.

Tokes ZA, Gendler SJ, Dermer GB

Dept. Biochemistry, Sch. Medicine, Univ. Southern California, Los Angeles, CA, 90033

J Supramol Struct Cell Biochem; 17(1):69-77 1981

The biosynthesis and release of glycoproteins were studied as a function of breast epithelial cell arrangement in vitro. Benign and malignant human surgical specimens were maintained in organ culture under conditions where the three-dimensional tissue integrity was least altered. In order to confirm the synthesis of alpha-1-chymotrypsin (ACHY) in organ cultures and to estimate the proportion of labeled glycoproteins present as the proteinase inhibitor, quantitative immunoprecipitation was performed on culture supernatants. It was found that 3.5 and 7.8% of the total labeled glycoproteins from two benign breast tissues were recognized as ACHY by specific antibodies. Similarly, 0.9-5.4% of the total labeled components was precipitated from supernatants of three infiltrating ductal carcinomas. ACHY may represent a protective shield of cell surface components on breast epithelia, modulating the effects of invading leukocytes. (21 Refs)

65. URINARY POLYAMINE EXCRETION DURING GROWTH AND REGRESSION OF 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED RAT MAMMARY CARCINOMA.

Anehus S, Albinsson A, Andersson G, Heby O

Dept. Zoophysiology, Univ. Lund, Helgonavagen 3b, S-223 62 Lund, Sweden

JNCI; 67(6):1265-1268 1981

The correlation of urinary excretion of polyamines and tumor mass was examined with the use of a controlled experimental model. Mammary carcinoma growth was induced in Sprague-Dawley virgin rats by intragastric administration of 7,12-dimethylbenz[a]anthracene. Tumors were palpable after about 45 days. After a period of growth, regression of the estrogen-dependent tumors was induced by bilateral ovariectomy. Tumor volume and 24-hr urinary excretion of polyamines were measured during the course of tumor growth and regression. Urinary polyamines were analyzed after acid hydrolysis to determine the total amount of bound and free polyamines. Putrescine excretion followed closely the changes in tumor volume during the course of tumor growth and regression. Urinary spermidine excretion, however, remained essentially unchange d in ovariectomized rats; spermine was barely detectable in any of the urines. There was a high positive correlation between the 24-hr urinary putrescine excretion and urine volume. In nonovariectomized rats, the mammary tumor(s) continued to grow. An unexpected result of the advanced tumor progression was that urinary excretion of both putrescine and spermidine decreased steadily with time as did urine volume. This phenomenon may be due to the fact that tumor-bearing rats develop a state of overt malnutrition, involving complex disturbances of the host metabolism, manifested in decreasing body wt. (Author abstract) (15 Refs)

66. CYTOPHOTOMETRIC ANALYSIS OF HUMAN CHORIOEPITHELIOMAS, MELANOMA, EWING'S SARCOMA, AND MAMMARY GLAND CARCINOMA TRANSPLANTED INTO ATHYMIC MICE. COMMUNICATION II.

Revazova ES, Petrova AS, Zubrikhina GN, Iudicheva TN
All-Union Cancer Res. Center, Moscow, USSR
Lab Delo; (11):668-669 1981

DNA content was studied in cells of human melanoma, Ewing's sarcoma, breast carcinoma, and chorioepithelioma transplanted into athymic mice. Pulse cytophotometric analysis showed the monomodal distribution of ploidy in Ewing's sarcoma cells; greater than 50% of cells had diploid DNA content. Majority of melanoma cells had triploid and tetraploid DNA content, while diploid cells comprised only 6.1% of cell population. Chorioepithelioma and breast carcinoma cells were characterized be marked heterogeneity. (3 Refs) (In RUS)

67. EFFECTS OF THIOTEPA ON PRIMARY CULTURES OF DMBA-INDUCED MAMMARY TUMOURS OF RATS: KINETICS AND ULTRASTRUCTURE.

Fink SM, Tseng MT
Dept. Anatomy, Univ. Louisville, Louisville, KY, 40292
Br J Cancer; 44(5):762-765 1981

Effects of thiotepa (TP) on growth kinetics, thymidine labeling index (LI), and fine structure of cells cultured from mammary tumors induced by 7,12-dimethylbenz(alpha)anthracene (DMBA) in female Sprague-Dawley rats were determined. Cell subpopulations of these tumors were separated by isopycnic centrifugation. Primary cell cultures were obtained from band 3. Of the three parameters measured, the most obvious TP (10(-2) 10(-6) M)-induced changes were in the rate of DNA synthesis as determined by LI. At 10(-2) M TP, none of the remaining attached cells incorporated (3H)thymidine during pulse labeling. While the percentage of cells in S phase closely approximated the percentage of attached cells after treatment with 10(-6) M TP, the LI curve declined more sharply than the dose-response curves. Ultrastructural analysis revealed no viable cells remaining after 10(-2) M TP. At the lowest TP concentration (10(-6) M), the cells could not be distinguished from controls on the basis of fine structure. Cell-kinetic data indicated that growth inhibition of the selected DMBA-induced tumor cell subpopulation in culture by TP is dose-dependen t. A good correlation was found between cell kinetics and labeling index. Indirectly, the study supports the concept of cell heterogeneity in solid tumors. (9 Refs)

68. RAT MAMMARY TUMOR CLASSIFICATION: NOTES ON COMPARATIVE ASPECTS.

Komitowski D, Sass B, Laub W
(c/o Sass) Registry Experimental Cancers, Div. Cancer Cause and Prevention, NCI, NIH, Bethesda, MD, 20205
JNCI; 68(1):147-156 1982

Mammary tumors (170 spontaneous and 1,613 induced with 7,12-dimethylbenz[a]anthracene) in inbred SD rats were classified histologically. The neoplasms were divided into three main categories: fibroepithelial, epithelial, and connective tissue. In the fibroepithelial category, compound tumors showing a wide range of histologic structures with variation in the arrangement of both epithelial and connective tissue elements that differ among lobules occurred in 44 (25.9%) spontaneous and 1,027 (63.7%) induced neoplasms, whereas fibroadenomas occurred in 41 (24.1%) untreated and 175 (10.9%) treated rats. Uncommon fissured tumors were found in 1 (0.7%) untreated and 6 (0.4%) treated animals, whereas carcinosarcomas were found in only 10 untreated animals. In the epithelial category, tubular adenomas occurred in 48 (28.2%) untreated and 164 (10.2%) treated animals. Cystadenomas, duct papillomas, intraductal carcinomas, and anaplastic carcinomas were found less frequently. Adenoacanthomas occurred in only 12 (0.8%) of the treated animals. Among tumors with a fibrous component only, fibromas occurred in 22 (13%) untreated and 97 (6.0%) treated animals. Fibrosarcomas were less frequent, occurring in 4 untreated (2.4%) and 54 (3.4%) treated animals. (Author abstract) (19 Refs)

REVIEWS AND OTHER RELATED STUDIES

69. MARKERS IN BREAST CANCER.

Sulitzeanu D
Lautenberg Center General and Tumor Immunology, Hebrew Univ.-Hadassah Medical Sch., POB 1172, 91120 Jerusalem, Israel
Isr J Med Sci; 17(9/10):865-868 1981

A large number of markers associated with breast cancer have been tested for potential usefulness in the initial diagnosis, the evaluation of prognosis, the detection of recurrence and the assessment of response to therapy. Useful but limited information has been obtained in some of the cases by measuring the levels of a number of markers such as carcinoembryonic antigen, ferritin and haptoglobin. None of the known markers are specific for breast cancer and no single marker is elevated in all patients with advanced disease. Studies with multiple markers may provide better coverage. A great deal of attention is being focused on the level of immune complexes that are found in 30 to 50% of the patients. It has been claimed that immune complex levels tend to rise in patients with advanced disease, but these claims await further confirmation. The only markers likely to be useful for early diagnosis are tumor-associated antigens (TAA). Sev eral putative TAA have been identified, but clinical trials employing TAA are still a long way off. Identification of breast cancer TAA may be facilitated by current analyses of immune complexes isolated from patients. Preliminary results of such analyses suggest that immune complexes recovered from patients with breast cancer may contain antigens not present in patients with nonmalignant diseases. (Author abstract) (19 Refs)

70. AN EPIDEMIOLOGICAL BASIS FOR CANCER CONTROL.

Armstrong B
NH and MRC Res. Unit in Epidemiology and Preventive Medicine, Univ. Western Australia, Dept. Medicine, Nedlands, Australia
Cancer Forum; 5(3):136-143 1981

Primary and secondary prevention of cancer, particularly cancer of the lung, breast, and colon and melanoma, which together account for greater than 40% of new cancer cases and premature mortality is discussed. Primary prevention aims at preventing cancer from occuring by ending exposure to the causal agent either by environmental or life type control. Lung cancer is attributable mainly to cigarette smoking; some cases result from occupational exposure. Breast cancer is associated with nulliparity, first full-term pregnancy at a comparatively late age, low parity, diet, radiation, post-menopausal estrogens, and oral contraceptives. Colon and rectal cancer are mainly related to dietary fiber deficiency and excess fat and meat consumption. Melanoma of the skin is due to exposure to UV radiation. Etiologies of other neoplasms are discussed: brain neoplasms (phenobarbitone use), prostate cancer (diet, cadmium exposure), stomach cancer (diet), leukemia (x-rays, benzene exposure, antineoplastic agent use), pancreatic cancer (diet, cigarette smoking), bladder cancer (occupational exposure to aromatic amines, cigarette smoking), and cervix cancer (sexual promiscuity). Dietary modification, cessation of smoking, and avoidance of excessive exposure to UV light was recommended. Screening methods involved in the secondary prevention of cancer include cervical cytology, proctosigmoidoscopy, and mammography at regular intervals for certain segments of the population. The choice between primary and secondary prevention of cancer is discussed. (20 Refs)

71. EPIDEMIOLOGY OF BREAST CANCER. PREVENTIVE ASPECTS.

Modan B
Dept. Clinical Epidemiology, Chaim Sheba Medical Center, 52103 Tel-Hashomer, Israel
Isr J Med Sci; 17(9/10):804-809 1981

Descriptive data demonstrate a marked variation in the incidence of breast cancer in distinct populations, which is closely linked to socioeconomic status and correlated with a differential age-specific incidence pattern and time trends. These suggest a westernization effect, and the possible existence of two distinct disease entities - pre- and postmenopausal. Known risk factors may be defined in a number of ways. From a preventive standpoint, a practical classification is suggested whereby risk factors are grouped as preventable, modifiable, unapproachable or spurious. The only risk factors which seem definite at present are estrogen exposure, family history and radiation, with the possible contribution of benign breast disease, replacement hormones, and diet. The only preventable factors are radiation and possibly long-term hormonal replacement, but their contribution to the disease incidence in the population is minimal. Two theoretically modifiable factors are diet and age at first birth, but the latter cannot be easily influenced, and the effect of dietary modification is still unsubstantiated. (Author abstract) (45 Refs)

72. THE ROLE OF HORMONES IN THE ETIOLOGY AND PREVENTION OF BREAST CANCER AND ENDOMETRIAL CARCINOMA.

Gambrell RD
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30912
Rev Bras Clin Ter; 10(9):671-678 1981

The roles of estrogens and progestogens in mammary and endometrial cancers were presented under the following headings: role of exogenous estrogens in endometrial cancer (EC), role of endogenous estrogens in EC, role of oral contraceptives (OCs) in EC, role of exogenous estrogens in mammary cancer (MC), role of endogenous estrogens in MC, and role OCs in MC. Administration of estrogen plus progestogen (EP) to menopausal women decreases the incidence of EC below that of untreated women. Postmenopausal women with increased endogenous estrogens should receive progestogens to reduce the risk of EC. OCs with EP in every tablet are protective against EC, while sequential administration provided less protection. MC is significantly less frequent in women receiving estrogens or EP than in postmenopausal women that never receive the hormones. OCs reduce the risk of benign mammary disease and give some protection against MC. Mortality rate due to MC is significantly lower in women who used OCs than in those who did not. (34 Refs) (In POR)

73. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.

Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

Human epidemiologic studies and supporting laboratory animal data on the relationship between nutrition and modification of cancer are reviewed. Carcinogenesis results from at least two steps: initiation and promotion. Diet, a major risk factor, can influence cancer in several ways. Food additives or contaminants can act as initiators, promoters, or inhibitors; nutritional deficiencies can cause biochemical changes. Nutritional excesses can cause metabolic changes which may then promote or inhibit cancer. A decrease in caloric intake leads to an increase in tumor latency and a decrease in the number of tumors. The incidence of breast cancer in humans is positively correlated with the consumption of animal protein, fat, and simple carbohydrates. Dietary fat also exerts a promotional effect on colonic cancer. Cancer of the prostate and pancreas is positively correlated with fat consumption, but the evidence is not absolute. Vitamin A apparently inhibits tumor formation during the promotional phase. Vitamin C does not manifest a clear protective effect against any cancer. Studies with selenium have produced disparate results, while nitrosamines have shown carcinogenicity in many species. In most cases nutrients modify rather than cause cancer. (100 Refs)

74. ENDOCRINOLOGICAL ASPECTS OF BREAST PHYSIOLOGY (MEETING ABSTRACT).

Robyn C
Human Reproduction Research Unit, Universite Libre de Bruxelles, Hopital Saint-Pierre, Brussels, Belgium
International Symposium on Endocrinology of Cystic Breast Disease, November 5-6, 1981, Turin, Italy, Italian Society of Endocrinology; 1981

Growth of the mammary gland is discontinuous; a first wave occurs at puberty under the influence of sex steroids, and the parenchymal breast tissue differentiates into a ductular-lobular-alveolar system. Growth slowly continues with each menstrual cycle up to the age of 30-35. A second major wave of growth takes place during pregnancy. Estrogens, progesterone and prolactin with variable relative potencies induce proliferation and differentiation of alveolar epithelial stem cells and control arborization of the ductular-lobular system. The interplay of the three hormones seems to be essential for optimal and balanced growth of the mammary tissue. From mid-pregnancy, the secretory differentiation of the alveolar stem cells is induced, predominantly under the influence of prolactin in synergism with metabolic hormones: this involves Messenger (m)-RNA synthesis for the production of milk proteins and enzymes. However, during pregnancy most of the secretory effects of prolactin are suppressed and lactation does not occur: in vitro, progesterone suppresses the prolactin effects of casein m-RNA synthesis. After delivery, progesterone, estrogens and placental lactogen abruptly drop and prolactin induces full secretory activity and milk release. Oxytocin is required for milk ejection. Prolactin and oxytocin are released by neuroendocrine reflexes initiated by suckling. Prolactin does not appear to be essential for maintaining lactation. In mothers nursing for 2 yr or more, hyperprolactinemia persists for 15-18 mo; it is associated with infertility due to anovulation or corpus luteum deficiency. The decline in serum prolactin levels seen in the mothers after 18 mo of lactation is not associated with a decline in milk yield, at least when considering the amount of milk per feeding. Finally, the sequence of the endocrine events controlling full differentiation of the breast tissue and the timing of their occurrence seem to be of decisive importance in the resistance of the mammary epithelium to carcinogenic agents. (no Refs)

75. ESTROGEN RECEPTOR CYTOCHEMISTRY IN HUMAN BREAST CANCER: STATUS AND PROSPECTS.

Nenci I
Istituto Anatomia Patologica, Universita di Ferrara, Ferrara 44100, Italy
Cancer; 48(12):2674-2686 1981

Advances in knowledge of the endocrine control of neoplastic growth can be expected to stem directly from advances in pertinent techniques. Following this theme, the present paper describes how recent development in cytochemical techniques for estrogen receptors may maintain this expectation and lead to significant progress in the basic knowledge of breast cancer that can influence the treatment approach. Cytochemical techniques have shown that the binding of estrogen to target cells and tissues can be specifically visualized: moreover, estrogen binding sites characterized cytochemically under controlled conditions have proved to fulfill the accepted criteria for estrogen receptors. Some working solutions to basic questions concerning the tumor hormone-responsiveness have been provided and more precise explanations of fundamental growth-regulatory mechanisms are expected to emerge from the approach to breast cancer by cytologic endocrinology. However, in the present state of the art and in spite of tantalizing bits of data, cytochemical techniques for estrogen receptors do not seem extensible to routine purposes, as alternative to biochemical receptor assays in selecting patients for endocrine therapy. One must have strong reservations on their clinical use because of the almost complete lack of information about correlations of cytochemical results with the response to endocrine therapy. More studies evaluating the practical validity of estrogen receptor cytochemistry are required. (Author abstract) (92 Refs)

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CHEMICAL CARCINOGENESIS

1. ETHYLENE OXIDE (ETO): EVIDENCE OF CARCINOGENICITY.
Coene RF
National Inst. for Occupational Safety and Health, Cincinnati, OH
Vet Hum Toxicol; 23(6):439-443 1981

DIETARY FACTORS IN CARCINOGENESIS

2. NUTRITIONAL ASPECTS OF CANCER PREVENTION: AN OVERVIEW.
Silverman J
American Health Foundation, Naylor Dana Inst Disease Prevention, Valhalla, NY, 10595
J Am Vet Med Assoc; 179(12):1404-1409 1981

3. FORMATION OF N-NITROSO COMPOUNDS IN FOODS.
Gray JI
Dept. Food Science and Human Nutrition, Michigan State Univ., East Lansing, MI, 48824
ACS Symp Ser; 174():165-180 1981

EPIDEMIOLOGY, ETIOLOGY AND GENETIC ASPECTS OF HUMAN CANCER

4. LYMPHOMAS AND LEUKAEMIAS. PART 2: TROPICAL AMERICA.
Jimenez E
Hospital Nacional de Ninos 'Dr. Carlos Saenz Herrera', Apartado 1654, San Jose, Costa Rica
Clin Haematol; 10(3):894-915 1981

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Olweny CL
Uganda Cancer Inst., P.O. Box 3935, Kampala, Uganda
Clin Haematol; 10(3):873-893 1981

6. MALIGNANT MELANOMA.
Creagan ET
Div. Medical Oncology, Mayo Clinic, Rochester, MN, 55905
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7. MELANOTIC TUMORS OF THE UVEA AND RETINA.
Schmitt H
Universitats-Augenklinik, Theodor-Stern-Kai 7, D-6000 Frankfurt am Main, W. Germany
Med Klin; 76(24):672-675 1981
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CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

8. THE NATURAL HISTORY OF CARCINOGENESIS: IMPLICATIONS OF EXPERIMENTAL CARCINOGENESIS IN THE GENESIS OF HUMAN CANCER.
Pitot HC, Goldsworthy T, Moran S
McArdle Lab. for Cancer Res., Dept. Oncology, Medical Sch., Univ. Wisconsin, Madison, WI, 53706
J Supramol Struct Cell Biochem; 17(2):133-146 1981

9. CURRENT CONCEPTS AND CONTROVERSIES IN CHEMICAL CARCINOGENESIS.
Weinstein IB
Div. Environmental Sciences, Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY, 10032
J Supramol Struct Cell Biochem; 17(2):99-120 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

10. BURKITT'S LYMPHOMA.
Ambrus JL, Ambrus CM
Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
J Med; 12(6):385-413 1981

11. PRIMARY HEPATIC CARCINOMA.
Iosquin CJ
Catedra de Medicina Interna A, Facultad de Ciencias Medicas, La Plata, Argentina
Rev Fac Cienc Med La Plata; 4(2):27-31 1981
In SPA

METHODOLOGY IN CARCINOGENESIS RESEARCH

12. MUTAGENESIS AND CARCINOGENESIS TESTING IN VITRO.
Casto BC
Northrop Services, Incorporated, P.O. Box 12313, Research Triangle Park, NC, 27709
Biotechnol Bioeng; 23(12):2639-2671 1981

OTHER REVIEWS IN CARCINOGENESIS

13. CANCER IN THE YEAR 2000. A REVIEW.
Saxen E
Suomen Syoparekisteri, Liisankatu 21 B, 00170 Helsinki 17, Finland
Duodecim; 97(20):1708-1716 1981
In FIN

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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HE 20.3173/2:

PREVALENCE OF BREAST CANCER IN HUMAN POPULATIONS

1. CANCER MORBIDITY IN NORTH-WESTERN INDUSTRIAL REGION OF THE SOVIET UNION.

Merabishvili VM, Serova LS
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Vopr Onkol; 27(12):3-8 1981

Cancer morbidity in the North-Western region (NWR) of the European part of the Soviet Union is reported. The overall morbidity index for NWR exceeded that for USSR; increased morbidity was recorded for both the urban and rural populations. In 1975, the incidence (per 100,000 persons) of lung cancer, colonic cancer, stomach cancer, breast cancer, and cervical cancer was 30.2, 76.9, 57.7, 12.5, and 2.9, respectively. The decrease of morbidity indices was recorded for cervical cancer, compared with the increase of breast cancer morbidity. (3 Refs) (In RUS)

2. BREAST CANCER IN CHILE.

Medina E, Marre B, Yrarrazaval M, Caris L, Medina AM
Departamento de Salud Publica, Facultad de Medicina, Universidad de Chile, Santiago, Chile
Rev Med Chil; 109(10):987-996 1981

Mortality due to mammary cancer (MC) in 1974-1975 varied from 2/100,000 in Costa Rica to 23/100,000 in England; in Chile, it was 4.5/100,000. MC mortality around the world is inversely related to birth rate. In Chile, the highest mortality rates due to MC were observed in Metropolitan areas and in Region V, which also have the lowest birth rates. Mortality rates for other cancers had been stable during the last 20 yr in Chile, while the mortality rate for the MC was increasing steadily (1.1/100,000 in 1930, 2.3/100,000 in 1950, and 4.6/100,000 in 1970). This increase in mortality rate due to MC was observed throughout Chile, with the highest values in Region V. Essentially this increase occurred in women greater than 45 yr old. The following aspects of the problem were discussed: diagnostic difficulties, relationship between the MC mortality rate and standard of living, family size, use of hormones, diet, exposure to different carcinogens, and risk factors. (33 Refs) (In SPA)

3. CANCER MORBIDITY IN USSR IN 1979 (ANALYSIS OF MORBIDITY INDICES).

Napalkov NP, Merabishvili VM, Tserkovnyi GF, Preobrazhenskaia MN
No affiliation given
Vopr Onkol; 27(11):3-27 1981

Cancer morbidity indices in the Soviet Union are summarized. An overall intensive index for 1979 was 201.6 per 100,000. A total number of newly detected cancers exceeded 530,000. Cancer morbidity in urban population was by 21.8% greater than that in rural population. The increase of morbidity indices was recorded for rectal cancer, lung cancer in men, skin cancer, breast cancer, and lymphatic and hematopoietic neoplasms. The decrease of morbidity indices was recorded for lip cancer, stomach cancer, and cervical cancer. There was no changes in the morbidity indices for esophageal cancer and lung cancer in women. The growth of prevalence index was indicative of the efficacy of the system of of cancer detection and follow-up. The overall index of 1-yr mortality was 35.4%. Absolute number of patients who died of cancer reached 366,400. The decrease of mortality indices was recorded for stomach cancer and cervix cancer. The increase of mortality indices was recorded for cancers of the mouth, pharynx, esophagus, rectum, larynx, lungs, br east, and urinary organs. (12 Refs) (In RUS)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

4. REPRODUCTIVE FUNCTION IN RELATION TO BREAST CANCER RISK.

Vorherr H

Dept. Obstetrics and Gynecology, Univ. New Mexico, Sch. Medicine, Albuquerque, NM

Excerpta Med Int Congr Ser; 551:224-233 1981

Factors which mediate breast cancer (BC) risk are discussed. While it has been reported that estrogens may decrease BC risk, in patients with estrogen-dependent BC they may accelerate malignant growth. While the proliferative action of estrone and estradiol have been linked to BC, the rise in BC incidence with advancing age parallels the gradual fall in estrogens. Estriol and 2-hydroxy-estrone protect the breast from estradiol-estrone hyperstimulation and carcinogenesis. Increased androgen conversion to estrone may stimulate epithelial proliferation of breast tissues toward overt carcinoma. Early menarche increases BC risk nearly twofold, while married women experience a twofold lower risk than unmarried women. Parous women have a two- to fourfold decrease in BC risk as compared to nonparous women. BC risk is increased in women undergoing late menopause. Bilateral ovariectomy before the age 40, early pregnancy, and extended lactation may protect against BC, while high parity coupled with early pregnancy, or late first pregnancy increase risk. (37 Refs)

5. RELATIONSHIP OF WEIGHT TO THE PROMOTION OF BREAST CANCER AFTER MENOPAUSE.

de Waard F, Poortman J, Cellette BJ

Dept. Epidemiology, Inst. Social Medicine, Utrecht, The Netherlands

Nutr Cancer; 2(4):237-240 1981

Epidemiologic and experimental evidence for a relation between high body wt and breast cancer is reviewed. A survey of the female population including 23,500 women 50 yr or older gave evidence for the initiation-promotion concept of breast cancer. Body wt and height were measured at each screening examination. Estrogen receptors (ER) were measured in 180/258 patients with breast cancer that was diagnosed during the survey. ER were found in 117 patients. The determination of ER-status of cancers has provided evidence that promotion in ER-positive cases is favored by obesity and inhibited by leanness. Estrogen-dependent breast cancer can be promoted by extra-ovarian estrogens from adipose tissue. The effect of wt and obesity is probably mediated through a menopausal estrogen mechanism. In lean postmenopausal women, clonal selection is thought to lead to a preponderance of ER-negative cells in cancer. Initiation of breast cancer is probably unrelated to obesity. Induction of breast cancer may be rare after menopause, but existing tumors grow if they receive stimuli to which they are sensitive. If wt reduction would prolong the free interval in breast cancer (until recurrence of secondaries), it would probably a lso be a means of controlling ER-positive breast cancer in its preclinical stages. (23 Refs)

6. LACK OF ASSOCIATION BETWEEN WEIGHT AND OESTROGEN RECEPTORS IN WOMEN WITH BREAST CANCER.

Mason B, Holdaway IM, Yee L, Kay RG
Dept. Surgery, Auckland Hosp., Park Road, Auckland 1, New Zealand
J Surg Oncol; 19(1):62-64 1982

Evidence for a relationship between body weight and tumor estrogen receptor (ER) level has been sought in women with newly diagnosed breast cancer. There was no significant correlation between body weight and tumor ER concentration, either over the whole of observed weight or when considering groups above or below a weight of 68 kg. Similarly, when women were subgrouped by prognostic variables such as nodal status, tumor size, or menopausal status, there was no significant relationship between ER level and body weight. These data suggest that observations linking breast cancer risk with increasing body weight cannot be explained by variations in ER level. (Author abstract) (10 Refs)

7. PSYCHOIMMUNOENDOCRINE CHARACTERISTICS OF LONG SURVIVAL WITH BREAST CANCER (MEETING ABSTRACT).

Gorzynski JG, Holland J, Massie MJ, Katz J, Zumoff B, Fukushima D, Bekesi G
Memorial Sloan-Kettering Cancer Center, New York, NY
Psychobiologic, Psychophysiologic, Psychosomatic, and Psychosocial Aspects of Neoplastic Disease, 4th International Symposium, June 2-6, 1981, Bressanone, Italy European Working Group for Psychosomatic Cancer Research 25 pp., 1981.

Ten yr ago 30 women were studied prior to breast biopsy for psychologic and endocrine state. They were studied for cortisol metabolite excretion rates, psychological defensive adequacy (using the Katz Defensive Adequacy Scale) and body wt. Following the biopsy, 22 women received the diagnosis of breast cancer, and 8 had benign disease. Ten yr later, 11 had died from breast cancer, and seven were located to participate in a follow up study of their psychoendocrine and immunologic state. Six of these women had negative nodal status; one had positive nodal status. Mean cortisol metabolite excretion rates, as determined prior to biopsy, were 5.9 mg/g creatinine for 7 surviving women and 4.3 mg/g creatinine for 11 women with breast cancer who died. Katz Defensive Adequacy Scale, as determined prior to biopsy, had a mean score of 2.7 for 11 women who died in the 10 yr period prior to follow up study and 6.3 for 7 surviving women (indicating greater failure of psychological defenses). Mean body wt at the time of biopsy was 142 pounds for 7 women who survived 10 yr and 179 pounds for those who died. Along with negative nodal status associated with long survival, these data suggest three additional psychoendocrine factors which contribute to long survival: lower body wt, greater psychologic defensive failure with greater emotional distress, and higher cortisol metabolite excretion rates. These findings suggest the need for further study of hypothalamic-pituitary-adrenal axis in women with breast cancer. (no Refs)

8. BREAST CANCER RISK (MEETING ABSTRACT).

Sitruk-Ware R
Department of Reproductive Endocrinology, Hopital Necker, 75015 Paris, France
Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

Benign breast diseases (BBD) and breast cancer appear to have the same hormonal environment. Particularly, a long period of exposure to a high estrogenic activity without a proper secretion of progesterone, as during the perimenarcheal period, has been reported as one of the most important factors for the development of breast disorders. To analyze the risk of breast cancer according to the duration of this 'estrogen window' we decided to begin a large prospective study gathering large cohorts of patients in different French departments. A standardized questionnaire has been presented to the French cancerologists and gynecologists to enroll patients and controls in this study according to the same protocol. In this questionnaire we paid particular attention to the symptoms related to a hormonal disequilibrium, to the duration of the first estrogen window and to the use of contraceptive drugs during this period. (no Refs)

9. HORMONAL GENESIS OF BREAST CANCER (MEETING ABSTRACT).

Mauvais-Jarvis P
Department of Reproductive Endocrinology, Hopital Necker, 75015 Paris, France
Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

This paper relates the different lectures given in December 9, 1980 by the speakers invited by the Breast Cancer Task Force Committee (Bethesda, MD) to participate in a workshop on luteal phase defects and breast cancer risks. The role of unopposed estrogen effect as a major promoting factor in human breast carcinogenesis is emphasized - particularly in terms of duration of exposure, especially during the first 'estrogen window' which precedes the first full term pregnancy. In the same conception, benign breast disease seems to be provoked by a progesterone insufficiency due either to the 'physiological' estrogen window occurring either after the beginning of breast development and during the perimenopausal period, or after stress exposure of women at any time of their reproductive life. In terms of prevention, the therapeutical use of progesterone and synthetic progestins in women presenting either a benign breast disease or a high risk of breast cancer is proposed in particular during the perimenarcheal period of the reproductive life. (no Refs)

10. LIFE STRESS EVENTS IN CANCER AND PSYCHIATRIC DISORDERS: A STATISTICAL EVALUATION IN 144 PATIENTS (MEETING ABSTRACT).

Conti C, Biondi M, Pancheri P
Universita di Roma, Viale Universita 30, I-00100 Roma, Italia
Psychobiologic, Psychophysiologic, Psychosomatic, and Psychosocial Aspects of Neoplastic Disease, 4th International Symposium, June 2-6, 1981, Bressanone, Italy European Working Group for Psychosomatic Cancer Research 25 pp., 1981.

Many studies have suggested a role of life stress events, in particular of 'emotional losses' in the multifactorial etiology of human neoplasms; only a few of these studies, however, report an objective evaluation of life stress events or report statistical comparision between cancer and control groups. Our research compared the incidence of life stress events over the ten yr period preceeding onset of illness in three groups of patients: 52 women with breast or cervical cancer in the first stage of the disease, 46 women with benign breast or uterine disease, and 46 women with neurotic disorders. To collect data on life events, patients completed two objective questionnaires for the assessment of stress events, the Schedule of Recent Experiences (SRE) of Rahe and Holmes and the Life Experience Survey (LES) of Sarason and Johnson. The first step in the comparison among the three groups was to draw up the 'av temporal profiles' of life events of the ten yr period preceeding disease onset, according to the four indexes derived from the LES (negative change score, positive change score, total change score) and from the SRE (life change units score). The three groups were then statistically compared for differences arising from the two scaling methods for three temporal intervals: from 0 to 3 yr preceeding disease onset, from 0 to 5 yr and from 0 to 10 years. Finally we carried out a chi-frequency analysis of 'emotional loss' events in the three groups of patients. (no Refs)

11. DETERMINATION OF A CONSTITUTIONAL PSYCHOSOMATIC FACTOR PROBABLY INFLUENCING TUMOR DEVELOPMENT IN MAN (MEETING ABSTRACT).

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Psychobiologic, Psychophysiologic, Psychosomatic, and Psychosocial Aspects of Neoplastic Disease, 4th International Symposium, June 2-6, 1981, Bressanone, Italy European Working Group for Psychosomatic Cancer Research 25 pp., 1981.

Experiments in animals: Rabbits were injected with pilocarpine. Some of them recovered slowly from the intoxication, others more quickly. Two groups were formed on the basis of difference in recovery time. Both groups were injected with tumor mass. The slow-recovery group showed a significantly greater sensibility for the inoculation than the other group. Investigations in cancer patients: Two variables were compared in patients given surgical treatment for breast cancer, gastric cancer, sarcoma or melanoma. The survival time after operation was compared with the morning 11-hydroxycorticosteroid ('cortisol') level one yr before the closing date of the study or death. Values up to 31 mugr % cortisol in the serum were associated with a better prognosis in patients with breast and gastric carcinoma. No correlation was found in sarcoma and melanoma. We then compared the values obtained the first day after admission with the next value, determined about 7 days later. The first hospital admission can be expected to be a rather strong factor of stress for our patients. Cortisol levels decreasing after admission to 31 mugr % or less showed a better prognosis in breast and gastric carcinoma patients. Finally we compared the prognosis of all values above 31 mugr % with values fluctuating around 31 mugr %. The latter group showed a better prognosis. Proposals: (1) As slow recovery from stress is a risk factor for some cancers, this factor could be estimated. This can be done in many ways, even at an early age. (2) Treatment influencing the psyche-hypophysis-adrenal cortex-thymus axis might be developed as adjuvant therapy of some cancers, as well as a method of prophylaxis of tumor development in appropriate cases. (no Refs)

12. INFLUENCE OF DIET ON MAMMARY CANCER.

Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
Nutr Cancer; 2(4):232-236 1981

Analysis of epidemiological data and experiments with animals have provided evidence that dietary fat has an important influence on mammary cancer. Epidemiological data on dietary fat in relation to breast cancer, mechanisms of action of dietary fat in mammary carcinogenesis, and effects of dietary components, other than fat, on mammary carcinogenesis are reviewed. The epidemiological data indicate that total dietary fat shows a better correlation with breast cancer mortality than either animal fat or fat derived from plant sources. More information on the relationship between diet and breast cancer will enable a better assessment of the potential value of the dietary approach to prevention or treatment. Restriction of calories from fat has value not only as a possible means of reducing cancer incidence, but also in decreasing the incidence of heart disease and obesity. (44 Refs)

13. EPIDEMIOLOGY OF BREAST CARCINOMA IV: AGE AND HISTOLOGIC TUMOR TYPE.

Rosen PP, Lesser ML, Senie RT, Duthie K
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
J Surg Oncol; 19(1):44-47 1982

The purpose of this study was to correlate major chronologic events known to have a bearing on the risk for developing breast carcinoma with histologic tumor type. Data were obtained for 1,024 consecutively treated patients with the seven most common forms of mammary carcinoma. The age of occurrence of the following events was determined: menarche; first marriage; first pregnancy and first childbirth; last pregnancy and last childbirth; diagnosis. The interval between each of these events and diagnosis of breast cancer was also calculated. Patients with medullary carcinoma had a significantly lower mean age at diagnosis than those with any of the other tumor types. Because of the lower mean age at diagnosis, medullary carcinoma patients were found to have significantly shorter intervals between age at diagnosis and the following: menarche, first pregnancy or first childbirth, and last pregnancy or last childbirth. Intervals between age at diagnosis and these other events were not significantly different among patients with other types of carcinoma. The ages of menarche, marriage, or pregnancy were not related independently to any tumor type. These data indicate that except for current age, the age of occurrence of major risk factors for developing breast cancer is unrelated to the histological type of tumor a patient develops. (Author abstract) (21 Refs)

14. BREAST PARENCHYMAL PATTERNS: ANALYSIS OF 332 INCIDENT BREAST CARCINOMAS.

Wolfe JN, Albert S, Belle S, Salane M
Dept. Radiology, Hutzel Hosp., 4707 St. Antoine, Detroit, MI, 48201
AJR; 138(1):113-118 1982

A detailed analysis of 332 incident breast carcinomas is presented. The study results indicate that there is validity to the breast parenchymal patterns as an indication of risk for developing breast cancer and that risk is independent of length of follow-up and age of patient. All cases were drawn from a referral-type practice at Hutzel Hospital, Detroit, Michigan. The cases were compared to controls for computation of relative risk up to and beyond a follow-up period of 48 mo. They were also compared to a consecutive series of prevalent breast carcinomas seen at Hutzel Hospital during the 6 yr 1975-1980. The extent of disease in the cases described in this report is somewhat more favorable than in a consecutive series of prevalent cancers operated on at Hutzel Hospital. Most breast cancers occur in the P2 breast, a smaller number in the DY, and only 12% in the combined N1P1 type. The conclusions of other investigators regarding parenchymal patterns as risk indicators are reviewed. Particular attention was paid to comparing the length of follow-up and age of patient. There was no diminution of proportions of cases in the P2/N1-P1 or DY/N1-P1 after a 48 mo follow-up. There was a significant diminution in the proportion of cases falling into DY/N1-P1 after age 50, and less so in P2/N1-P1. Furthermore, relative risk was unaffected by time or age. (Author abstract) (13 Refs)

15. RISK FACTORS OF BREAST CANCER AMONG PATIENTS HAVING A BREAST TUMOR (MEETING ABSTRACT).

Clavel B, Brunet M, Le Moize F, Goupil A

Centre R. Huguenin, Saint-Cloud, France

Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

A study of breast cancer risk factors has been conducted on a sample of 2,300 women treated in the Centre Rene Huguenin for benign (2/3 of the patients) or malignant tumors (1/3 of the patients). Among the malignant tumors a significatly greater frequency of breast cancer in the mother, the sister or among the children was observed. The same higher frequency was also found in lack of pregnancy, a first pregnancy after 35 yr, obesity, or a previous breast cancer. In the benign population a higher frequency of breast cancer in the mother's mother, a previous benign breast tumor, and the use of contracetptive pills were observed. Breast cancer in the father's mother or mother's aunt, having sisters, first menstruation before 11 yr and first pregnancy after 35 yr were not significantly different between the two groups. (no Refs)

16. STUDY OF BIOPSIED BENIGN BREAST DISEASE IN WESTERN AUSTRALIA (MEETING ABSTRACT).

Fleming NT, Armstrong BK, Sheiner HJ

Department of Surgery, University of Western Australia, Adelaide, Australia

Clinical Oncology Society of Australia, November 24-27, 1981, Melbourne, Australia. The Society 70 pp., 1981.

The purpose of the study was to establish the incidence of biopsied benign breast disease in the female population of Western Australia and to study its descriptive epidemiology by using pathology reports and a Hospital Morbidity Survey (HMS) listing for the whole State. There were 1,283 females who had biopsied benign breast disease in 1978 which means a crude incidence rate of 290 per 100,000 females over 15 yr of age. The rates for three main histological categories were as follows: Benign Mammary Dysplasia 184/100,000, Fibroadenoma 63/100,000 and Other Benign Conditions 43/100,000. The largest proportion of biopsies were for women under 55 yr of age with the highest rate occurring between ages 30-49 yr. In these age groups, the incidence of breast cancer is still relatively low. Analysis of personal characteristics showed that biopsy rates were higher in never-married compared with ever-married females, in women resident in the Perth area compared with those outside, and in Australian born females compared with those born in Southern Europe. Women working in 'Professional' and allied occupations had higher rates than those in other occupations and there was a suggestion of a trend for higher rates in higher socioeconomic groups. In a concurrent study of Breast Cancer in Western Australia there were parallel findings for all of the above characteristics except that there was no difference in rates according to area of residence. (no Refs)

17. ASSOCIATION OF CHRONIC MYELOCYTIC LEUKAEMIA AND BREAST CANCER (MEETING ABSTRACT).

Anagnou J

No affiliation given

Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Albeit co-existence of chronic myelocytic leukemia (CML) followed by breast cancer and vice versa is exceedingly rare, we observed three such cases during 1980. In the first case, a 73 yr old woman developed breast cancer 12 mo after the diagnosis of CML. The CML had not been treated. In the second case, a 52 yr old woman developed breast cancer 22 mo after diagnosis of CML and therapy with a total dosage of only 132 mg Busulphan. In the third case, a 60 yr old woman developed CML 20 mo after the diagnosis of breast cancer treated surgically as well as with irradiation and adjuvant chemotherapy. In all three cases the Philadelphia chromosome was positive, the LAP-Score was zero or very low and no evidence of bone metastases was present. On the basis of the data it is difficult to draw any conclusions regarding the development of the second malignancy and its possible pathogenetic relation to therapy with cytostatics and irradiation. Indeed, an etiological relationship between therapy and occurrence of the second malignancy could be suggested only in the second and third case. Nevertheless, even in the third case it seems improbable, in view of a known latent period of approx 4 yr from the initiation of cancer chemotherapy to the development of a second neoplasia. Most probably, the second malignancy in all three patients must be considered either a chance occurrence or a result of genetic predisposition to malignancy rather than from the carcinogenic therapy potential. (1 Ref)

18. CANCER EPIDEMIOLOGY.

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Rev Infirm; 31(17):19-27 1981

Standardized cancer mortality rates for 1973 yr set France in third place, behind West Germany, England, and Wales. In France, the overall cancer mortality was 221 per 100,000 inhabitants but men were affected twice as often as women. The increase of cancer mortality rate from 1954-1976 was attributed to the increase in cancer deaths among men due to lung cancer and cancers of the upper gastrointestinal and pulmonary tracts. Deaths from cancer represented about 20% of general mortality and a third of the deaths for men in the 55-75 yr range and for women in the 35-55 yr range. Analytical epidemiology has determined the probable causative factors of various types of cancers. These etiological agents include tobacco, pollution, ultraviolet or ionizing radiation, alcohol, nutrition, hormones, infections, immunology, and genetic factors. Cancer has also been linked to certain immunosuppressive and cytotoxic drugs. Resistance to epidemiological data is steadfast not only because pleasurable pursuits such as drinking and smoking are involved but also because the economic consequences of change are staggering. However, more than half of the cancer cases would be affected by alcohol and tobacco campaigns and by the early screening and treatment of cancers of the breast and uterus. (17 Refs) (In FRE)

POSSIBLE IATROGENIC FACTORS IN HUMAN BREAST CARCINOGENESIS

19. BREAST CANCER AND USE OF ANTIHYPERTENSIVE DRUGS AND ORAL CONTRACEPTIVES: RESULTS OF A CASE-CONTROL STUDY.

Clavel F, Le M, Laplanche A

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Bull Cancer (Paris); 68(5):449-455 1981

A case control study in breast cancer was conducted in France between 1976 and 1980. One thousand thirty-one patients with histologically confirmed cancer of the breast were entered into the study. Each was matched on age (+-5 yr) to two controls hospitalized in the same clinic for a benign disease. We have specially studied the anti-hypertensive drugs, and the oral contraceptives. We found no difference between cancer patients and controls concerning their consumption of anti-hypertensive drugs, whether containing reserpine or not, and their consumption of oral contraceptives. However, there is a relation between the use of oral contraceptives and the age, family status and social class of women. After adjustment on these factors, we found a 1.62 relative risk of developing a cancer of the breast among the women using oral contraceptives (p less than 0.02). (Author abstract) (37 Refs) (In FRE)

20. INCIDENCE OF SECOND MALIGNANCIES IN HODGKIN'S DISEASE AFTER VARIOUS FORM OF TREATMENT (MEETING ABSTRACT).

Armand JP, Delsol G, Pris J, Combes PF

Centre Claudius-Regaud, 11 rue Piquemil, Toulouse 31052, France

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

This retrospective evaluation was undertaken to verify the incidence of second malignancies in a group of patients with Hodgkin's disease (HD). Patients (332) were staged and treated in Toulouse from 1963 to 1978. Most (271) of them had a 3 yr follow up in 1980 and were documented for this study. The incidence of acute non lymphoid leukemia (ANLL) and solid tumor (ST) was evaluated after various types of treatment including: Radiotherapy alone (RT), Radiotherapy and chemotherapy (CT), and chemotherapy alone. During this period only MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) or rarely COPP (cyclophosphamide + OPP) or MOPP + bleomycin were used as a first line treatment. ABVD (Adriamcyin, bleomycin, vincristine, dacarbazine) was only used after failure of 3 courses of MOPP. Nine patients out of 271 have presented a second malignancy. Five ANLL were documented in adults (2 males, 3 females), 2 had RT only, 2 (RT + CT), 1 CT only. Four ST were documented (3 males, 1 female) they included lung, head and neck, bladder and breast cancer. All malignancies were discovered 3 to 10 yr after diagnosis of the HD. Four malignancies (out of those 331 HD), all ST, were detected prior to HD (one to 72 mo before) and cured (2 skin, 1 head and neck, 1 colon). Although Procarbazine and alkylating agent are an essential factor in a second malignancy, RT and genetic factor have to be taken into account. (no Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

21. REACTION OF THE ENDOCRINE SYSTEM OF FEMALE RATS OF DIFFERENT AGE ON ADMINISTRATION OF 75SE-SELENOMETHIONINE.

Dedov VI, Norets TA
Res. Inst. Medical Radiology, Obninsk, USSR
Med Radiol (Mosk); 26(11):48-52 1981

Long-term effects of 75Se-selenomethionine were studied in 3 and 12-14 mo old random-bred female rats. Radionuclide administration caused persistent hyperfunction of the thyroid, inhibition of the glucocorticoid function of the adrenals, and estrus disorders. The females with persistent estrus developed mammary gland tumors and pituitary adenomas. The yield of tumors in older rats was higher than that in young animals. (6 Refs) (In RUS)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

22. EFFECT OF SELENIUM ON GROWTH RATE OF CANINE MAMMARY CARCINOMA CELLS IN ATHYMIC NUDE MICE.

Watrach AM, Milner JA, Watrach MA
Dept. Veterinary Pathobiology, Univ. Illinois, Urbana, IL, 61801
Cancer Lett; 15(2):137-143 1982

The effect of selenium on tumor growth in nude mice inoculated with canine mammary carcinoma cells was examined. In two experiments, mice were injected in the left thorax with 5 x 10(6) tumor cells and then received sodium selenite (2 ug/g body wt) in phosphate-buffered saline (PBS) or PBS alone. In experiment 1 selenium was injected intrathoracically 3x/wk over a 23-day period, whereas in experiment 2 selenium was administered sc 3x/wk over a 32-day period. Tumor growth rate in selenium-treated animals was retarded 75% in experiment 1 and 76% in experiment 2. Total tumor, liver, and kidney weights were significantly lower in selenium-treated animals than in controls. Total RBC and WBC counts, Hb, hematocrit, and total protein levels were not significantly different in untreated and selenium-treated tumor-bearing animals. When selenium-treated tumor-bearing and non-tumor-bearing (intact) mice were compared, total body wt was not affected in intact mice but was reduced approx 10% in tumor-bearing mice. Selenium concentrations in the blood and liver were higher in tumor-bearing than in intact mice after selenium treatment. The data indicate that selenium inhibits the growth of canine mammary tumor transplanted in athymic nude mice. (23 Refs)

23. LACK OF EFFECT OF DIETARY FAT ON THE GROWTH AND ESTROGEN SENSITIVITY OF THE MT-W9B TRANSPLANTABLE MAMMARY TUMOR.

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Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Nutr Cancer; 3(1):27-34 1981

Effects of diets containing low- (LF: 0.5%) or high (HF: 20%) fat on the growth and estrogen responsiveness of the

MT-W9B mammary tumor in Wistar-Furth rats were studied. Tumor growth was not significantly affected by HF or LF diet. Tumor growth was also unaffected in either group by ovariectomy (OVx), sham OVx, or by OVx with estradiol supplementation. Dietary fat intake did not alter the sensitivity of the uterus to estrogen. Progesterone receptor (PR) levels were slightly elevated in tumors from sham-OVx rats fed a HF diet compared those fed a LF diet; this increase was not statistically significant. Responses of PR to OVx or to OVx with estrogen supplementation were not altered by dietary fat levels. PR levels were decreased in OVx rats to 16% and 14% of control levels in LF and HF groups, respectively, and increased 16-fold and 13-fold, respectively, in OVx rats given estradiol. In the same tumors, estrogen receptor levels were not significantly altered by either dietary or hormonal manipulation. PR levels were elevated in uteri from sham-OVx rats fed a HF diet compared to those fed a LF diet when expressed on a picomole/uterus basis, but this increase was not statistically significant when expressed on a per mg basis. Dietary fat did not appear to affect the response of uterine PR to estrogen manipulation. Dietary effects on estrogen receptors are described. The results suggested that dietary fat does not influence the sensitivity of normal or neoplastic tissue to estrogen action. (37 Refs)

24. MAMMARY CARCINOMA INDUCED BY ORAL ADMINISTRATION OF ETHYL METHANESULPHONATE. DETERMINATION OF SOME OF THE PARAMETERS AFFECTING TUMOR INDUCTION.

Ueo H, Takaki R, Yamagami H, Sugimachi K

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Carcinogenesis; 2(12):1223-1228 1981

The carcinogenic activity of ethyl methanesulfonate (EMS), an alkylating agent and a potent mutagen, was examined in Wistar King A and Sprague Dawley rats following oral administration. In the Wistar King A rats, mammary carcinomas were detected in all of the young female rats by the 32nd wk after initiation of the experiment. To determine the optimal experimental conditions for the rapid and invariable induction of mammary carcinomas, the relationship among age, sex, strain of the rats and concentration and duration of EMS administration, and tumor production was investigated. The tumor incidence was higher in the younger female rats and the Wistar rats were more susceptible than Sprague-Dawley rats. Mammary carcinomas were also induced in the younger male rats. In addition, concomitant production of renal tumors occurred by the 40th wk in young rats administered 10(-2) M or 2 x 10(-2) M of EMS soln, while renal and uterine tumors developed concomitantly in the older female rats given 3 x 10(-3) EMS by the 56th wk. Histologically, the prevailing features of tumors were infiltrating ductal adenocarcinoma in the mammary glands, mesenchymal tumor in the kidney, and leiomyosarcoma in the uterus. Methyl methanesulfonate, an analogue of EMS, did not induce tumors in any organs. (Author abstract) (7 Refs)

25. DDT ACCELERATION OF MAMMARY GLAND TUMORS INDUCED IN THE MALE SPRAGUE-DAWLEY RAT BY 2-ACETAMIDOPHENANTHRENE.

Scribner JD, Mottet NK

Pacific Northwest Res. Foundation, 1124 Columbia St., Seattle, WA, 98104

Carcinogenesis; 2(12):1235-1239 1981

The compound 2-Acetamidophenanthrene (AAP) yields adducts to rat liver DNA and RNA in amounts comparable to those found for the potent hepatocarcinogen 2-acetamidofluorene, but is not hepatocarcinogenic. This suggested that AAP might initiate liver tumors, but was incapable of causing their progression to a detectable state. To test this hypothesis, the protocol devised by Peraino was used, in which 21-day-old male Sprague-Dawley rats were fed 0.02% AAP in a grain diet for 3 wk. This was followed by long-term feeding of 0.05% 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane (DDT). The mean latent period of all tumors (primarily mammary tumors) was reduced about 6 mo by the DDT feeding. No tumors were found in rats treated with DDT only. Livers in all animals appeared normal at autopsy or on laparotomy, and showed barely detectable signs of toxicity upon histological examination. Thus, we have found that a once wide-spread environmental chemical acts as a tumor accelerator on a major target for human tumors. Because this finding is in the male rat, the significance of this result for breast cancer in women is uncertain. (Author abstract) (15 Refs)

26. ENHANCED INHIBITION OF MAMMARY CARCINOGENESIS BY COMBINED TREATMENT WITH N-(4-HYDROXYPHENYL)RETINAMIDE AND OVARIECTOMY.

McCormick DL, Mehta RG, Thompson CA, Dinger N, Caldwell JA, Moon RC

Lab. Pathophysiology, Life Sciences Div., IIT Res. Inst., Chicago, IL, 60616

Cancer Res; 42(2):508-512 1982

Bilateral ovariectomy and dietary administration of the retinoid N-(4-hydroxyphenyl)retinamide (4-HPR) are both effective inhibitors of chemical carcinogenesis in the rat mammary gland. The present study was designed to determine whether an enhanced inhibitory effect is obtained with combined ovariectomy and 4-HPR administration, compared to either treatment alone. In separate experiments, 50-day-old virgin female Sprague-Dawley rats received either a single iv injection of 50 mg N-methyl-N-ni trosourea per kg body wt or a single intragastric dose of 20 mg 7,12-dimethylbenz(a)anthracene. The experimental design was the same in both the N-methyl-N-nitrosourea and 7,12-dimethylbenz(a)anthracene experiments: Group 1, 25 intact rats, placebo diet; Group 2, 25 intact rats, supplement of 782 mg 4-HPR per kg diet; Group 3, 50 ovariectomized rats, placebo diet; Group 4, 50 ovariectomized rats, supplement of 782 mg 4-HPR per kg diet. Feeding of the 4-HPR supplement was begun 7 days after carcinogen administration; ovariectomy was performed 7 days post-7,12-dimethylbenz(a)anthracene or 14 days post-N-methyl-N-nitrosourea. In both experiments, combined ovariectomy plus 4-HPR was significantly more active in suppressing mammary cancer induction than was either manipulation alone. 4-HPR was a more effective inhibitor of carcinogenesis in ovariectomized rats than in intact animals. These data indicate that 4-HPR is highly effective in inhibiting ovarian hormone-independent cancers and suggest that retinoid inhibition of mammary carcinogenesis does not involve an influence on ovarian hormone action. (Author abstract) (19 Refs)

27. GENETIC COMPONENT IN RAT MAMMARY CARCINOGENESIS.

Vogel HH, Turner JE
Dept. Radiation Oncology, Univ. Tennessee Center for Health Sciences, 800 Madison Ave., Memphis, TN, 38163
Radiat Res; 89(2):264-273 1982

Mammary tumor induction following whole-body irradiation of rats of five different genetic strains was investigated. Female rats were exposed as young adults to 50 rad fission neutrons, with a neutron-to-gamma ratio of about 7. After 1 yr, single mammary tumors were found in 56% of Long-Evans and Sprague-Dawley strains; palpable mammary tumors were found in 25-29% of the Buffalo and Fischer-344 strains, but in only 5% of the Wistar-Lewis strain. Only one tumor was found in 73 unirradiated controls. Mammary tumors appeared much earlier in rats exposed to fission neutrons than in control rats. No evidence was obtained that mammary neoplasms increased with age. The order of sensitivity among the five strains tested and the percentages of rats developing mammary tumors within 1 yr did not change from the first radiation experiments (about 70 days) to the fourth replicate experiment (about 200 days of age). Chi square analysis of tumors induced after 1 yr shows a highly significant strain difference: sensitivity in decreasing order was Long-Evans; Sprague-Dawley; Buffalo; Fischer; and Wistar-Lewis. Most tumors were adenofibromas or fibroadenomas, both benign. The total of all five strains for diagnosed adenocarcinomas in the first yr after irradiation was 36%. Nearly half the mammary neoplasms were first found between days 300 and 365 after exposure. (20 Refs)

28. EFFECT OF AN ESTROGEN ANTAGONIST (TAMOXIFEN) ON THE INITIATION AND PROGRESSION OF GAMMA-IRRADIATION-INDUCED MAMMARY TUMORS IN FEMALE SPRAGUE-DAWLEY RATS.

Welsch CW, Goodrich-Smith M, Brown CK, Miglorie N, Clifton KH, Goodrich-Smith M, Brown CK, Miglorie N, Clifton KH
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
Eur J Cancer Clin Oncol; 17(12):1255-1258 1981

One hundred and sixty-eight female Sprague-Dawley rats were divided among four groups (42 rats/group) and were irradiated with 400 rad [137Cs] gamma rays to the whole body when 59 days old. The estrogen antagonist tamoxifen was injected sc daily from 29-89 days of age (Series 1) or from 89-149 days of age (Series 2), prior to the onset of palpable mammary tumors. Two groups of rats were injected with the diluent and served as controls. All rats were palpated bi-weekly for mammary tumors and killed 37 wk after gamma-irradiation. The number of mammary carcinomas which developed in each group and their significance levels were: series 1, controls, 31; tamoxifen treated, 11, p less than 0.01; series 2, controls, 33; tamoxifen treated, 17, p less than 0.01. Tamoxifen treatment did not significantly influence the incidence of benign mammary tumors (fibroadenomas) nor the rate of body wt gain. Thus, the effective use of an estrogen antagonist for the prophylaxis of radiogenic mammary carcinomas has been demonstrated in this study. (Author abstract) (13 Refs)

29. DEHYDROEPIANDROSTERONE: AN ANTI-OBESITY AND ANTI-CARCINOGENIC AGENT.

Schwartz AG, Hard GC, Pashko LL, Abou-Gharbia M, Swern D
Fels Res. Inst., Temple Univ., Philadelphia, PA, 19140
Nutr Cancer; 3(1):46-53 1981

Effects of long-term administration of dehydroepiandrosterone (DHEA) on female C3H-Avy/A (obese) and C3H-A/A (non-obese) mice were examined. DHEA treatment significantly inhibited wt gain in both strains of mice without suppressing food consumption. Food consumption of the DHEA-treated C3H-A/A mice was significantly greater than that of controls. DHEA significantly reduced the rate of breast cancer development. From 12 to 18 mo of age, the difference in breast cancer rates between controls and DHEA-treated C3H-A/A mice was significant. In the C3H-Avy/A mice, significant differences in breast cancer rates between controls and DHEA-treated mice were evident between 10 and 15 mo. The C3H-Avy/A control mice experienced a marked enhancement in rate of breast cancer development when compared to the C3H-A/A control group. A single ip injection of DHEA (15 mg/kg) inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA) stimulation of 3H-thymidine incorporation in mouse epidermis. DHEA also blocked the TPA stimulation of 3H-thymidine incorporation in a rat kidney epithelial cell line; the inhibition was reversed by culturing for 20 hr in medium without DHEA. The results suggest that DHEA has an anti-carcinogenic effect and may have pharmacologic value in cancer prevention. (29 Refs)

30. STRESS SEVERITY AND ADRENAL FUNCTION IN THE DEVELOPMENT OF THE DMBA-INDUCED RAT MAMMARY TUMOR: SOME PRELIMINARY INDICATIONS (MEETING ABSTRACT).

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Psychobiologic, Psychophysiologic, Psychosomatic, and Psychosocial Aspects of Neoplastic Disease, 4th International Symposium, June 2-6, 1981, Bressanone, Italy European Working Group for Psychosomatic Cancer Research 25 pp., 1981.

One hypothesis which has appeared in several forms is that the function relating severity of presumably stressful stimulation (PSS) to animal tumor development is J-shaped, with mild PSS inhibiting, and severe PSS promoting tumor development. Our findings to date suggest that there can be genuine differences among mammary tumor systems in their responses to PSS; that increasing PSS severity does not change the response of the dimethylbenzanthracene (DMBA) induced rat mammary tumor (DMBA-RMt) from inhibition to enhancement; that severe, protracted adrenocortical activation need not indicate a particular tumor response to PSS; and that WBC levels are not strongly related to the response of the DMBA-RMt to PSS. Adrenal and thymus wt have regularly failed to suggest protracted adrenal corticoid responses to PSS which inhibits the DMBA-RMt. In mice, treatments which promoted and which failed to affect mammary tumors produced equal reductions in thymus/adrenal wt ratio. Diazepam, which suppresses the rise in corticosterone elicited by PSS, has produced at best a marginal blockage of the PSS effect on th DMBA-RMt in our experiments. Adrenalectomy promoted by the DMBA-RMT, but a second experiment - still in progress - suggests that adrenal demedullation may also promote this tumor. WBC counts were done in three recent experiments ; the severe restraint, adrenalectomy, and diazepam experiments. In no case did leukocytopenia accompany aversive treatments. This again suggests the absence of long-term adrenocortical response to PSS which inhibits the DMBA-RMt. There was, in fact, some indication of higher WBC counts in animals exposed to PSS. This is consistent with, but does not require, an immunological explanation of the tumor's inhibition by PSS. (no Refs)

31. FORMATION AND REMOVAL OF 7,12-DIMETHYLBENZ[A]ANTHRACENE-NUCLEIC ACID ADDUCTS IN RAT MAMMARY EPITHELIAL CELLS WITH DIFFERENT SUSCEPTIBILITY TO CARCINOGENESIS.

Tay LK, Russo J
Experimental Pathology Lab., Dept. Biology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
Carcinogenesis; 2(12):1327-1333 1981

The susceptibility of the rat mammary gland to 7,12-dimethylbenz[a]anthracene (DMBA)-induced carcinogenesis is max when DMBA is fed to young virgin rats, diminishing with increasing age an d becoming almost nil when pregnancy and lactation occur prior to carcinogen administration. This present study was carried out to determine whether these differences in susceptibility to DMBA are related to the ability of the gland to form and/or remove DMBA-nucleic acid adducts. Primary mammary epithelial cell cultures derived from young virgin (YV), old virgin (OV) and parous (P) Sprague-Dawley rats were treated in vitro with [3H]-DMBA for 24 hr. Hydrolysates of DNA isolated from these cells were chromatographed on Sephadex LH-20 columns. In cells from the three groups of animals, the chromatographic profiles were qualitatively similar with three 3H-labeled products eluting in the region expected for hydrocarbon-nucleoside adducts. This similarity in profiles suggested that identical DMBA-nucleic acid adducts are generated in each group. The chromatographic data are also consistent with the hypothesis that the hydrocarbon-DNA adducts of DMBA were generated through reactions of a 'bay-region' diol-epoxide of DMBA with DNA. Excision of DMBA-DNA adducts was investigated by measuring the time-dependent decrease in specific activity of the less dense parental DNA peak following centrifugation on alkaline CsCl gradients. Within 48 hr post-DMBA treatment, P cells removed approx 36% of the adducts from DNA with YV and OV cells removed only 24% and 12% of the adducts respectively. In addition, P cells excised the adducts at a rate 1.5 and 5x faster than either YV or OV cells. These results suggest that the lower susceptibility of the parous rat towards DMBA-induced carcinogenesis may be due not to the generation of different DMBA-DNA adducts, but to a more efficient DNA repair mechanism that is the result of increased gland differentiation through the process of pregnancy and lactation. (Author abstract) (56 Refs)

32. EPIDEMIOLOGICAL FEATURES OF FELINE MAMMARY CARCINOMA.

Hayes HM, Milne KL, Mandell CP
Environmental Epidemiology Branch, NCI, NIH, Bethesda, MD
Vet Rec; 108(22):476-479 1981

Epidemiological features of cats with mammary carcinoma were studied. In a group of 132 cats with one or more mammary tumors, 113 had carcinomas of various types (including two males). Adenocarcinoma was the predominant cell type. Thirty females with mammary carcinoma had metastases, primarily in the lung (13) or lymphatic system (9). Five cats with carcinoma had a prior or concomitant history of viral infection: feline leukemia (2), viral rhinotracheitis (2), or viral pneumonitis (1). Relative risk (RR) analysis showed significantly less risk for spayed females (RR = 0.6) than intact females (RR = 1), however both groups showed increasing risk with advancing age. The Siamese breed had a significantly higher risk (RR = 2.0) than all other female cats combined (RR = 1) and did not show significantly increasing risk after 7-9 yr of age. Unlike humans and dogs, mammary tumors in the cat are not strongly associated with ovarian tumors. Estrogen receptors were not found in 90% of cat breast tumors, suggesting a particular suitability for evaluating therapeutic regimens for non-estrogen dependent breast cancers. (28 Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

33. EFFECT OF ESTRADIOL ON THE ULTRASTRUCTURE OF THE MCF7 HUMAN BREAST CANCER CELLS IN CULTURE.

Vic P, Vignon F, Derocq D, Rochefort H
(c/o Rochefort), U 148, Institut National de le Sante et de la Recherche Medicale, 60 Rue de Navacelles, 34100 Montpellier, France
Cancer Res; 42(2):667-673 1982

We have analyzed the effect of estradiol and of two classes of antiestrogens on the morphology of the MCF7 human breast cancer cell line by scanning and transmission electron microscopy. Estradiol progressively increased the number and the length of microvilli at the cell surface. The density of the microvilli network increased between 2 and 11 days of estrogen treatment, while the cells became more globular and less tightly attached to the surface of the dish. Estradiol also progressively transformed cells into secretory cells containing, at Day 2, large, clear mitochondria and, at Day 4, rough endoplasmic reticulum and Golgi complexes. At Day 6, secretory granules (diameter, 0.2 um), which mainly contained glycoproteins, were first observed in the cytoplasm. By Day 8, they were concentrated at the cell membrane and being liberated into the medium. Larger granules (diameter, 0.8 um), which probably contained lipids, were observed later (Day 11). Cell cultures in 10% fetal calf serum not treated by charcoal contained secretory granules. The modifications were induced by physiological concentrations of estradiol but not 5alpha-dihydrotestosterone. Progesterone (10 nM for 8 days) completely inhibited the effect of estradiol on the microvilli and secretory activity. Tamoxifen or hydroxytamoxifen did not induce secretory activity but did alter the cell morphology compared to control cells. The effects of estradiol were observed in other estrogen receptor-positive breast cancer cell lines (ZR 75-1, T 47 D) but not in an estrogen receptor-negative cell line (BT 20). This morphological evidence that estrogens modify the cell surface of breast cancer cells in culture and transform them into 'secretory cells' complements evidence that they induce the release of a glycoprotein with a mol wt of approx 50,000 into the culture medium. (The mol wt was found first to be 46,000. It seems to be closer to 52,000 in a 10% polyacrylamide gel and by using the NEN-labeled proteins as mol wt markers.) (Author abstract) (30 Refs)

34. ESTROGEN REGULATION OF GROWTH AND SPECIFIC PROTEIN SYNTHESIS IN HUMAN BREAST CANCER CELLS IN TISSUE CULTURE.

Edwards DP, Adams DJ, McGuire WL
Dept. Medicine, Univ. Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX, 78284
Adv Exp Med Biol; 138:133-149 1982

New protein markers of estrogen action and dependence of progesterone receptors upon estrogen-stimulated cell growth were studied using MCF-7 human breast cancer cells in tissue culture. Results showed that estradiol stimulates DNA polymerase activity in normal target tissues. Progesterone receptor induction and estrogen-mediated cell division may involve separate control mechanisms. A specific 24,000 mol wt protein may be a marker of estrogen-stimulated growth of human breast tumor cells. (27 Refs)

35. SUBNORMAL 24-HOUR MEAN CONCENTRATION AND ABNORMAL 24-HOUR PROFILE OF PLASMA LH IN THE LUTEAL PHASE IN WOMEN WITH BREAST CANCER.

Zumoff B, Levin J, Kream J, Strain GW, Markham M, Fukushima DK
Clinical Res. Center, Montefiore Hosp. and Medical Center, Bronx, NY, 10467
Anticancer Res; 1(5):305-308 1981

Twenty-four-hr mean plasma luteinizing hormone (LH) levels were measured in 14 otherwise healthy women (31-52 yr old) with breast cancer (BC) and in 13 healthy regularly cycling women (22-51 yr old). Seven of the patients (6 with localized and 1 with metastatic disease) and nine of the controls were in the follicular phase (FP); seven of the patients (5 with localized and 2 with metastatic disease) and four of the controls were in the luteal phase (LP). Follicular LH levels in the control women ranged from 10-23 milli (m)IU/ml. Five of the seven patients studied during FP had LH levels within the normal range, but the other two had markedly subnormal levels (4.4 and 7.4 standard deviations below the normal mean). LP levels in controls were 11-26 mIU/ml. One of the LP cancer patients had 11 mIU/ml; the other six had levels that were below normal (3.6-9.6 mIU/ml). The difference from the normal mean was significant. The 24-hr plasma LH profiles of five BC patients in LP were clearly abnormal: both frequency and amplitude of the episodic secretory pulses were markedly subnormal. Subnormal mean LH levels and abnormal plasma LH profiles may represent a human counterpart of the slow-gonadotropin-releasing hormone-pulsing model described in primates, indicating a type of hypothalamic dysfunction that might antedate the development of BC or might be a consequence of the disease. (22 Refs)

36. PLASMA LEVELS OF THYROXINE AND TRIIODOTHYRONINE IN WOMEN WITH BREAST CANCER.

Zumoff B, O'Connor J, Levin J, Markham M, Strain GW, Fukushima DK
Clinical Res. Center, Montefiore Hosp. and Medical Center, Bronx, NY, 10467
Anticancer Res; 1(5):287-291 1981

Plasma thyroxine (T4) and triiodothyronine (T3) levels were measured in women with breast cancer (BC). Two groups of BC patients were studied, one consisting of 29 women rigorously select ed (21 with localized disease, 8 with metastatic disease) and the second of 43 consecutive unselected women with BC in all stages. Three control groups were studied, one consisting of 22 women with other than breast cancer, the second of 21 women with miscellaneous noncancerous illnesses, and the third of 27 healthy women. Twenty-four-hr plasma T3 and T4 levels in the normal women and in the selected BC patients showed no significant difference between the groups with respect to T3 concentration but a marked, significant difference between the groups with respect to T4 level. Cancer patient T4 levels were greater by 33%. The mean 8 a.m. 'spot' plasma T4 level in unselected BC patients was 8.8 ug/deciliter, a significant 21% elevation above the level in normal women. The values for women with other than breast cancer and with miscellaneous non-cancerous illnesses were essentially identical to the value of women with BC, ie significantly elevated above normal levels. BC patients as a group show significant hyperthyroxinemia; this finding may represent a second nonspecific abnormality of thyroid hormone disease after hypotriiodothyroninemia. (39 Refs)

37. COMPOSITION OF THE ALPHA-DIHYDROTESTOSTERONE FRACTION DERIVED FROM ANDROSTENEDIONE INCUBATIONS WITH HUMAN BREAST CARCINOMA AND BENIGN PROSTATIC HYPERTROPHY TISSUE (MEETING ABSTRACT).

Killinger DW, Davis S, Perel E
Department of Medicine, Wellesley Hospital and University of Toronto, Toronto, Ontario, Canada
Fertil Steril; 36(2):267 1981

In previous studies of the metabolism of androstenedione (A) and testosterone (T) in breast adipose and carcinoma tissue, a significant amount of radioactivity was isolated in a fraction migrating with 5alpha-dihydrotestosterone (DHT) in several thin-layer chromatography (TLC) systems. Recrystallization data indicated that this fraction was not homogeneous. In the present study 3H-A (20 x 10(6) dpm) was incubated with a homogenate of breast carcinoma tissue with adenosine triphosphate (ATP) and nicotinamide-adenine dinucleotide phosphate (NADPH) as cofactors. The neural fraction was obtained following phenolic partition and purified by TLC. The DHT fraction was further purified by repeated TLC and the products identified by recrystallization to constant specific activity. The DHT fraction constant specific activity. The DHT fraction contained 7.9% of the starting material. Recrystallization data revealed that 26% of this fraction was androsterone, 8% etiocholanolone, 2% DHT, 0.4% epiandrosterone and 0.05% 5beta-androstan-3alpha-ol-17-one. In a smiliar study using 3H-A as substrate in an incubation with human benign prostatic hypertrophy tissue, 32% of the radioactivity migrated with DHT. In this fraction 30% was androsterone, 6% epiandrosterone, 4% DHT, 0.1% etiocholanolone, and 0.1% 5beta-androstan-3alpha-ol-17-one. These studies show that androsterone is a major intracellular metabolite of A in both breast and prostatic tissue. They also emphasize that the DHT isolated by TLC following incubation studies may contain several metabolities. (no Refs)

38. ESTROGEN SULPHURYLATION AS AN ALTERNATIVE INDICATOR OF HORMONE DEPENDENCE IN HUMAN BREAST CANCER (MEETING ABSTRACT).

Pewnim T, Adams JB, Ho KP
University of New South Wales, Sydney, New South Wales, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

A great many studies have now demonstrated that the evaluation of the estrogen receptor (ER) in human mammary cancer tissue is of considerable use in predicting response to hormone ablative, or hormone additive, treatments. One other biochemical parameter which has been shown to be related to prognosis and response to hormone ablation, is the assessment of steroid sulphurylation in the tumor. Accordingly, we have measured both ER status and estrogen sulphurylation in some 62 human primary carcinoma specimens. While no differences between ER positive and ER negative tumors were found in the synthesis of the active sulphate donor (3'-phosphoadenosine-5'-phosphosulphate), formation of estradiol-3-sulphate, catalyzed by estrogen sulphotransferase, was significantly higher in ER positive tumors. By choosing a discriminating value for estrogen sulphurylation of 40, then 16/19 of the ER negative tumor were below this point. Previous data had shown that 20/23 progesterone receptor negative tumors were also below this value. Since a knowledge of progesterone receptor status, coupled with ER status, considerably improves the chance of successfully predicting hormone dependency, measurement of estrogen sulphurylation may possibly provide an alternative simple method for evaluating hormone responsiveness in mammary cancer. (no Refs)

39. FEEDBACK EFFECTS OF MAMMARY GLAND TUMORS ON THE HOST PITUITARY PROLACTIN CELL.

Hymer WC, Signorella A
Biochemistry Program, Pennsylvania State Univ., University Park, PA, 16802
Adv Exp Med Biol; 138:251-286 1982

Differences in pituitary glands of animals bearing the 13762 and 3230 transplantable mammary gland adenocarcinomas and in vitro characteristics of the prolactin cells prepared from these two models were studied. Results are consistent with the hypothesis that the tumor exerts negative feedback at the pituitary or hypothalamic level and suggested that decreased prolactin cell function in animals bearing certain mammary tumors ultimately favors metastatic activity of the tumor cell. (35 Refs)

40. URINARY MELATONIN LEVELS IN HUMAN BREAST CANCER PATIENTS.

Bartsch C, Bartsch H, Jain AK, Laumas KR, Wetterberg L
Fichtenweg 6/110, D-7400 Tubingen 1, W. Germany
J Neural Transm; 52(4):281-294 1981

Urinary melatonin levels (UML) were measured to investigate the link between the pineal gland and breast cancer from the therapeutic and analytical angle. Studies were conducted with melatonin since it is the best documented hormone of the pineal gland. UML were measured in postmenopausal women in advanced stages of breast cancer and compared with controls. Melatonin excretion patterns of cancer patients were not synchronized as compared to patterns of controls. Results suggest that pineal melatonin secretion may be modified quantitatively and rhythmically in breast cancer patients. (40 Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

41. BCA (BREAST CANCER ANTIGEN). PRELIMINARY BIOCHEMICAL AND IMMUNOCHEMICAL STUDIES (MEETING ABSTRACT).

Accinni R, Ballo M, Cavalca V, Botta M, Bartorelli A
Univ. of Milano, Milan, Italy
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

In previous investigations we pointed out a carcinoembryonic antigen (CEA)-like antigen in a breast cancer pool, otherwise absent from control normal breast tissue. After demonstrating its different distribution in 48 primary breast carcinomas, we exploited a carcinoma pool, with high antigenic content, to extract BCA by means of 3M KCl. Subsequently, the antigen was purified by concanavalin A-Sepharose and bioabsorption chromatography, and labelled with Na 125I to be employed as tumor marker in the radioimmunoassay (RIA). Its physico-chemical and immunological characteristics, especially compared with those already well known for CEA, were analyzed. Preliminary High Performance Liquid Chromatography (HPLC) studies, on TSK 3000 and TSK 4000 columns (Trade Mark of Toyosoda), showed substantial differences in the retention times, therefore in the hydrodynamic vol, pointing out a complex stereochemical structure both for BCA and CEA. Differences in the isoelectric points were detected for these acidic glycoproteins by isoelectric focusing. Agar immunodiffusion, RIA and immunoperoxidase investigations showed interesting analogies and substantial differences for these two tumor markers. Besides, by applying on TSK 4000 columns CEA-positive sera, employed as experimental model, we observed that the antigen is eluted with the same retention time as the antigen extracted and purified from liver metastases. (no Refs)

42. COMPARISON OF SERUM BLOCKING FACTORS ON LEUKOCYTE ADHERENCE INHIBITION AND PHA LYMPHOCYTE BLASTOGENESIS IN BREAST CANCER PATIENTS.

Fujisawa T, Yonemoto RH, Waldman SR
Dept. Surgery, Inst. Pulmonary Cancer Res., Chiba Univ. Sch. Medicine, 1-8-1, Inohana, Chiba 280, Japan
Jpn J Surg; 11(6):406-412 1981

Correlation between specific and nonspecific blocking factors, and tumor burden in patients with breast cancer (BC) were studied. Modified leukocyte adherence inhibition (LAI) assay and phytohemagglutinin-induced blastogenesis assay were used in the study. Serum blocking factors (SBF) in sera from 48 patients with BC were examined. Specific SBF in LAI assay were detected in 15/21 patients with recurrence, in 5/11 with local or regional involvement, and in 3/16 with no evidence of the disease (NED). Significant differences were found between patients with recurrence of the disease and patients with NED. SBF in LAI and lymphocyte blastogenesis (LB) correlated in 29/48 patients; 9/48 SBF positive in LAI and LB, 20/48 SBF negative in LAI and LB. SBF in LAI was demonstrated in 14/48 patients whose sera showed no SBF in LB. Results indicate that SBF in LAI and LB are either induced or derived from BC tissue. SBF in LAI correlates closely with the tumor burden. SBF in LB shows less correlation. LAI assay shows good potential use as routine clinical test for detection of cell-mediated immunity. SBF, directed to tumor-associated antigens, shows potential use for evaluation of immunocompetence, residual tumor burden, and as a guide to therapeutic effects in cancer patients. (21 Refs)

43. IMMUNOLOGICAL CHANGES IN INFLAMMATORY CARCINOMA OF THE BREAST (MEETING ABSTRACT).

Plagne R, Chassagne J, Lafaye C, Chollet P, Ferriere JP
Centre J. Perrin, Clermont-Ferrand, France
Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

Eighteen patients with inflammatory carcinoma of the breast (stage II) vs 22 non inflammatory carcinomas of the same local extent were studied before any treatment, for cell mediated immunity and immune complexes. No significant changes were observed in these two groups, vs normal controls for lymphocyte total count E, EA, EAC rosettes, HTLA, Ia, OKT4, OKT 8 and suppresive activity measured by inhibition of blastogenesis of allogenic cells treated by phytohemagglutinin (PHA). In the two carcinoma groups, the lymphocyte electrophoresis showed a slight increase in the subsets of slow and intermediate mobility. Lymphocyte blastogenesis with PHA was significantly decreased in non inflammatory carcinomas but to a lesser degree in inflammatory carcinomas. Autorosettes were high in the two groups. Antibody dependent cellular cytotoxicity (ADCC) was significantly reduced in inflammatory cases but natural killer (NK) activity was normal. Immune complexes assayed but labeled Clq were increased in 30% of patients in each cancer group. So it does not appear that general immunological changes can explain the peculiar clinical pattern of this cancer nor its very poor prognosis. (no Refs)

44. DETECTION OF CELL-MEDIATED IMMUNITY (CMI) TO TUMOUR ASSOCIATED ANTIGENS OF ALLOGENIC EXTRACTS OF TUMOUR BY LYMPHOCYTE STIMULATION ASSAY (MEETING ABSTRACT).

Simo Camps E, Vich JM, Bofill D, Grau A, Manresa JM, Anguiz A
Servicio de Medicine Interna, Residencia Sanitaria 'Virgen de la Cinta', Tortosa, Spain
Sixth Meeting of the International Society of Haematology, European and African Division, August 30-September 4, 1981, Athens, Greece. Hellenic Society of Haematology 409 pp., 1981.

Between November 1979 to January 1981 we studied the cell-mediated immunity (CMI) to tumor associated antigens of allogenics extracts of tumors by lymphocyte stimulation assay in 24 cancer patients and 15 healthy controls. Blood samples were obtained of the cancer patients and healthy controls, each patient's WBC were tested for reactivity with appropiate tumor extracts: gastric cancer, ovary cancer, endometrium cancer, breast cancer and lung cancer. The fresh tumor extracts were prepared by technic described by Davis et al. Of the 24 cancer patients, 16.6% (4/24) gave positive specific lymphocyte stimulation assay and 25% (6/24) reacted non-specifically. Only 6.6% (1/15) healthy controls gave positive reactions. These results provide evidence for type-specific tumor-associated antigens in man, and for host reactivity can be employed in immunodiagnosis. (no Refs)

45. RADIOIMMUNOASSAY (RIA) IN PRIMARY BREAST CANCER: TISSUE AND PLASMA DETERMINATIONS (MEETING ABSTRACT).

Bartorelli A, Biancardi C, Ferrara R, Bailo M, Cavalca V, Accinni R
Istituto di Imunologia Clinica, Universita di Milano, Milan, Italy
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

We found a variable carcinoembryonic antigen (CEA)-like activity (RIA) in 80% of 48 primary breast carcinomas, singularly extracted (3 M KCl). Non-tumor tissues turned out negative. In the tissues with CEA-like activity indirect immunoperoxidase (PAP) showed cytoplasmic and membrane positivities stronger with antisera raised against BCA (Breast Cancer Antigen: CEA-like glycoproteins isolated form primary breast cancer tissue) than with those against CEA. The ratio between these two antisera is reversed when they are tested (PAP) against colon adenocarcinoma metastases. The difference in the immunological activity (RIA) between CEA and BCA is about 500-fold. Therefore a RIA technique, highly sensitive was developed to determine BCA extracted and partially purified, (bioabsorption chromatography, High Performance Liquid Chromatography) from 25 ml of plasma of each patient. (no Refs)

46. LYMPHOCYTOTOXIC ANTIBODIES IN CANCER.

Schocket AL, Malesky EV, Kohler PF
Div. Clinical Immunology, Dept. Medicine, Univ. Colorado Health Sciences Center, 4200 East Ninth Ave., Denver, CO, 80262
Cancer Immunol Immunother; 12(1):43-47 1981

Cold-reactive lymphocytotoxic antibodies (LCA) were measured in sera from 71 patients with various malignancies and 31 healthy controls. Cytotoxicity indices were elevated much more frequently in the sera from lymphoreticular malignancy (LM) patients (10/24) than in the sera from chronic lymphocytic leukemia (0/9), melanoma (5/22), carcinoma (1/16) of the breast, bowel, lung, or uterus patients, or those from normal controls (1/31). In the LM group LCA levels were not correlated with delayed hypersensitivity skin tests, skin croton oil response, total lymphocytes, T cells, or B cells. While LCA is apparently increased in patients with LM, the response is evidently not related to defects in the cell-mediated immune system in some of the patients. (36 Refs)

47. RELATIONSHIP BETWEEN IMMUNE RESPONSE AND SPONTANEOUS MAMMARY TUMOR RISK IN C3H/BI MICE (MEETING ABSTRACT).

Dufer J, Benoist H, Bouchet C, Desplaces A, Saracino RT
Centre Rene Huguenin, 5 rue Gaston Latouche, Saint-Cloud, France
Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

Immune reactivity has been explored in C3H/Bi MTV+ female mice, before and after onset of spontaneous mammary carcinoma. In vivo tests: immune response against T dependent (Sheep RBC and Oxazolone) or T independent antigens were performed along with in vitro studies on splenocytes: phytohemagglutinin (PHA) mitogenicity and Antibody Dependent Cellular Cytotoxicity (ADCC). Mice were separated into three groups: 2-4 mo old mice with low immediate risk of cancer, 5-6 mo old mice with high immediate risk and tumor bearers. In vivo immune response to SRBC and ADCC was impaired in 5-6 mo mice whereas PHA response was enhanced. All these values return to a normal level after tumor onset. These data seem to indicate that immune reactivity could be modified in C3H/Bi mice with high immediate risk of mammary carcinoma. (no Refs)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

48. DETECTION OF ANTIBODIES TO THE MOUSE MAMMARY TUMOR VIRUS BY AN ENZYME-LINKED IMMUNOASSAY IN SERA OF HUMAN BREAST PATIENTS (MEETING ABSTRACT).

Lidereau R, Amione J, Prieur S, Saracino RT
Centre René Huguenin, 35, Rue Dailly, 92211 Saint-Cloud, France
Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

An enzyme linked-immunoassay (ELISA) has been developed to detect antibodies to mouse mammary tumor virus (MMTV) in human sera. The MMTV prepared by centrifugation on gradient of saccharose is coated in microplates. After washing the plates, we incubate the sera diluted 1:10 in PBS (phosphate buffered saline) tween 0.5%, then the human goat-prepared anti-immunoglobulin coupled with alkaline phosphatase, and the substratum of alkaline phosphatase. The amount of antibodies present is revealed by measurement of its alkaline phosphatase activity. We have treated 44 control sera and 220 human breast cancer sera. We have not detected anti-viral antibodies in any control sera but in our patients we found 15% positive sera; we have no results about benign sera. These are preliminary results and must be interpreted with caution as long as the viral preparation is not perfectly purified. (no Refs)

49. SEQUENCE COMPLEXITY OF POLYADENYLATED RNA IN HUMAN BREAST CARCINOMA CELLS.

Arya SK
Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
Int J Biochem; 14(1):19-24 1982

Human breast carcinoma cells (line ZR-75-31; passage 60-80) were harvested from subconfluent monolayers and the complexity of total and polysomal polyadenylate (poly(A)) containing (poly(A)+) RNA was investigated by RNA:complementary (c)DNA and RNA:single-copy (sc) DNA hybridization. Kinetics of poly(A)+ RNA:cDNA hybridization suggested a 3-component solution; the overall sequence complexity of cellular poly(A)+ RNA was apparently about 200,000 kilobases (kb), and of polysomal poly(A)+ RNA about 38,000 kb. Hybridization of polysomal poly(A)+RNA with its cDNA showed a slightly different distribution sequence when cultures were treated with 0.2 ug/ml ovine prolactin for 48 hr. At maximal hybridization attained, 4.8% of sc DNA hybridized with total cellular poly(A)+RNA, and in a similar experiment 1.6% of polysomal poly(A)+RNA hybridized with scDNA. Results of cellular DNA:cDNA hybridization suggest that approx 5% of the sequences in total cellular and 15% of the sequences in polysomal poly(A)+RNA were reiterated transcripts. (26 Refs)

50. ALTERED METHYLATION OF ENDOGENOUS VIRAL PROMOTER SEQUENCES DURING MAMMARY CARCINOGENESIS.

Breznik T, Cohen JC
Dept. Microbiology and Immunology, Tulane Univ., Sch. Medicine, New Orleans, LA, 70112
Nature; 295(5846):255-257 1982

The methylation pattern of mouse mammary tumor virus (MMTV) was examined. Origin of the 2.1-and 1.4-kilobase (kb) HpaII fragments was determined by comparing MspI digests from various inbred mouse strains. Comparison of MspI digestion of DNA from the CBA/CaJ mouse strain (which includes units II and III) with that obtained with DNA from BALB/c (which includes units I, II, and III), indicated that the 2.1-and 1.4-kb MspI-HpaII fragments are derived from the subgenomic unit I. HpaII digestion of DNA from BALB/c mammary tumor 1247 produced several virus-specific fragments in addition to those derived from unit I, indicating that demethylation of other endogenous proviruses has occurred in this tumor. The origin of additional sites of demethylation in tumor 1247 was identified by EcoRI-HpaII double digestions. Demethylation of proviral units during tumorigenesis could be ascertained by determining which EcoRI bands are sensitive to further cleavage by HpaII. Results showed that the methylation pattern of endogenous virus sequences is specifically altered during tumorigenesis in uninfected mice. In addition to transformation by promoter insertion which may occur during exogenous MMTV infection, carcinogenesis by promoter derepression may occur; such an event is suggested by the observed demethylation of either the defective MMTV sequence (unit I) or specifically the 3' half of the nondefective proviruses (units II and III). (20 Refs)

51. DETECTION OF TYPE-SPECIFIC ANTIGENIC DETERMINANTS OF MURINE MAMMARY TUMOR VIRUSES WITH CELL-MEDIATED IMMUNE ASSAYS.

Lopez DM, Sigel MM, Schlom J
Univ. Miami, Miami, FL, 33101
Proc Soc Exp Biol Med; 169(1):144-148 1982

Cell-mediated immune assays were used to detect type differences among mouse mammary tumor viruses (MMTV) obtained from various mouse strains. The diversity of MMTVs found and their recognition by the lymphoid cells may explain variations in mouse mammary tumor development and differences in their metastatic potential. (23 Refs)

RADIOLOGICAL ASPECTS OF MAMMARY GLAND CARCINOGENESIS

52. PATHOLOGICAL EFFECTS OF LOW DOSES. LOW LINEAR TRANSFER ENERGY RAYS.

Dousset M
7, rue de la Gruerie, F 9190 Gif-sur Yvette, France
J Radiol; 62(11):556-560 1981

Somatic and genetic effects of low doses of low linear transfer energy are discussed in view of the diagnostic and therapeutic use of radiation. Prospective and retrospective studies relating radiation dose and effects are described. Findings on individuals exposed to irradiation at Hiroshima and Nagasaki are presented. With low dose radiation, there appears to be a curvilinear relationship between dose and effect with no threshold phenomenon. In experimental animals, irradiation prior to nidation results in the loss of the fertilized egg due to lack of implantation. During the first 35 days of human pregnancy, irradiation can result in malformations in the embryo. Fetal exposure to irradiation has been shown to increase the incidence of malignant disease. Radiation doses of greater than 100 rads can cause growth retardation among children irradiated prior to age 6 yr. An increased incidence of thyroid cancer has been observed among children less than 10 yr old exposed to low dose radiation. Adult exposure to radiation has been related to leukemia and cancers of the breast, thyroid, respiratory tract, bone, and digestive tract. Genetic effects of radiation are discussed. Male germ cells seem to be more sensitive to radiation than those of females. Germinal cells show varying sensitivities to radiation. (28 Refs) (In FRE)

53. THE BIOLOGICAL EFFECTS OF LOW-LEVEL IONIZING RADIATION.

Upton AC
Inst. Environmental Medicine, New York Univ. Sch Medicine, New York, NY
Sci Am; 246(2):41-49 1982

The biological hazard resulting from exposure to low-level ionizing radiation (IR) is discussed. IR occurs as electromagnetic or particulate radiation and may have a low or high rate of linear energy transfer (LET). IR may produce early transitory effects and/or late carcinogenic or heritable effects. Occurrence of nonheritable effects is apparently dose-rate-related and displays a threshold effect. Heritable effects apparently increase with total dose and display no threshold effect. Low-LET IR is more likely to produce simple forms of DNA damage that are likely to be repaired by cellular mechanisms when the IR dose rate is low. High-LET IR is more likely to produce more serious DNA damage that is more likely to be incorrectly repaired or remain unrepaired. Analysis of studies in animals and in three groups of humans (survivors of atomic bombings, patients undergoing radiological medical procedures, and those receiving occupational exposure to IR) shows an increase in breast cancer and leukemia with total exposure to IR. No heritable genetic damage has been demonstrated among children of atomic bomb survivors. Current data indicates that naturally occurring background IR accounts for 1-3% of all cancer fatalities, and that risks resulting from occupational exposure are small compared with other risks in daily life. (no Refs)

54. RADIATION RISKS IN INFANTS AND CHILDREN.

Faure C

Service de Radiologie, Hopital Trousseau, 8 a 28 avenue du Dr. Arnold-Netter, F 75710 Paris Cedex 12, France

J Radiol; 62(11):566-567 1981

Somatic and genetic risks associated with radiation of newborns, infants, and children are discussed. The association of thyroid cancer and low dose radiation of the thyroid during childhood for thyroid adenomas or hyperplasia and of breast cancer and childhood irradiation for scoliosis provides evidence for increased cancer risk among irradiated children. Childhood irradiation also has been related to an increased incidence of leukoses. The genetic risks of irradiation are similar in adults and children. Factors related to increased somatic risk in irradiated children are discussed. (11 Refs) (In FRE)

55. SCREENING FOR BREAST CANCER IN A HIGH-RISK SERIES.

Woodard ED, Hempelmann LH, Janus J, Logan W, Dean P

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J Surg Oncol; 19(1):31-35 1982

A unique cohort of women at increased risk of breast cancer because of prior x-ray treatment of acute mastitis and their selected high-risk siblings were offered periodic breast cancer screening including physical examination of the breasts, mammography, and thermography. Twelve breast cancers were detected when fewer than 4 would have been expected based on age-specific breast cancer detection rates from the National Cancer Institute/American Cancer Society Breast Cancer Demonstration Detection Projects. Mammography was positive in all cases but physical examination was positive in only three cases. Thermography was an unreliable indicator of disease. Given the concern over radiation-induced risk, use of low-dose technique and of criteria for participation that select women at high risk of breast cancer will maximize the benefit/risk ratio for mammography screening. (Author abstract) (12 Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

56. ARE RECEPTORS MARKERS OF PRECANCEROUS DISEASE IN BENIGN BREAST LESIONS (MEETING ABSTRACT).

Concolino G, Marocchi A, Picardi C

University of Rome, Rome, Italy

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Eleven benign breast tumors (BBT) (fibroadenoma) were investigated for the presence of estradiol receptor (ER), progesterone receptor (PR) and androgen receptor (AR) both in the cytosol and in the nuclei of the cells, in order to get information on the possibility of malignant derangement of such lesions. The dextran-coated charcoal was rountinely employed: total ER were measured with the single step exchange-extraction with sodium thiocyanate, while PR and AR were measured using 3H-R5020 and 3H-R1881 with the addition of sodium molybdate. It was found that nuclear steroid receptors are present only in 27.3% of BBT (3/11), while the percentage of positive nuclear determinations for breast carcinoma was found to be 66.7%. ERc was present only in 3, while ERn was never detected in the 11 BBT studied. PRc was present in 6 and PRn in 2 of the 11 BBT examined. AR was the most frequently found, being present in the cytosol of 7 and only in 1 nuclear fraction of the BBT studied. We want to remark that BBT with only cytoplasmic receptors can be treated with hormone therapy, while BBT with cytoplasmic and nuclear receptors may be indicative of a 'high risk' of cancer and therefore should be treated with surgical removal of the tumor. (no Refs)

57. MEASUREMENT OF CYTOSOL 17-BETA-OESTRADIOL (ER) AND PROGESTERONE (PR) RECEPTORS IN 200 PRIMARY BREAST CANCER SPECIMENS. RELATIONSHIP TO PRE VS. POST-MENOPAUSAL AGE AND TO AXILLARY NODE INVOLVEMENT (MEETING ABSTRACT).

Ros A, Biondani P

Clinical Ostetrica e Giecologica, Universita di Padova, Padua, Italy

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

We evaluated 200 specimens or primary breast cancer. In all women we observed following: pre- postmenopausal age, ER and PR quantitative measurement by charcoal-dextran assay and axillary node involvement. At surgical examination there were 71 women and 129 women in pre- and postmenopausal age res pectively. We considered as positive receptor values higher than 3 fM/mg of proteins. Distribution of both receptors was: ER+ PR+: 46%; ER+ PR-: 21%; ER- PR+: 5%; ER- PR-: 33%. We did not obtain any significant correlation between axillary node involvement in pre vs postmenopausal age, between receptor measurement in pre-vs postmenopausal age and between receptor content in involved vs not involved axillary node specimens. The presence of both receptors was higher in 1-2 metastatic node specimens (60%) than in the 3 or more metastatic node ones (38%). (no Refs)

58. ESTRADIOL AND PROGESTERONE RECEPTORS (ER, PGR) AND PROGNOSIS IN OPERABLE BREAST CANCER (MEETING ABSTRACT).

Cheix F, Asselain B, Noel P, Mayer M, Saez S

Centre Leon Berard, 28 rue Laennec, Lyon, France

Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

The presence of progesterone receptors in primary breast cancer was found to be correlated with a favorable prognosis in 148 patients with operable breast cancer. The difference in metastasis free survival is significant. This fact is independent of other prognosis variables such as age, menopausal status, tumor, node, metastasis (TNM) classification, axillary node status, grading. In the invasive galactophoric group progesterone receptors keep a prognostic value. Measurement of estradiol receptors (307 including the previous 148 patients) was found to be less effective for guiding the prognosis of operable breast cancer; but in the positive axillary node patients ER- cases relapse earlier than ER+. Combined evaluation of estradiol and progesterone receptors (ER, PgR) provide the same information as evaluation of progesterone receptors alone. (no Refs)

59. STEROID RECEPTORS: CORRELATION WITH HISTOLOGICAL FEATURES AND EARLY RECURRENCE OF BREAST CANCER (MEETING ABSTRACT).

Howat JM, Barnes DM, Swindell R, Harris M, Sellwood RA

Departments of Surgery and Pathology, University of South Manchester, Manchester, England

UICC Conference on Clinical Oncology, October 28-31, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Estrogen and progesterone receptors (ER and PR) were measured in the cytol of 231 primary breast cancer. No correlation was found between the presence of receptors and cellularity or histological type but there was a correlation between PR and elastosis and a trend towards a correlation between ER and elastosis. There was an inverse correlation between lymphocytic infiltration and both ER and PR. ER and PR were significantly more common in well differentiated (grade I) than in undifferentiated (grade III) infiltrating duct tumors. One hundred and seventy five patients in whom receptor status was known had modified radical (Patey) mastectomy. At a median follow-up of 24 months the overall recurrence rate was significantly lower in patients whose tumors contained ER compared with those who had no ER. There was no significant difference between the recurrences rates of tumors with and without PR. When analyzed with regard to axillary node involvement, it was only those patients with relatively few involved nodes (1-3) who benefitted by haveing ER. Possession of ER made no significant difference to the recurrence rates in patients without axillary metastases or those with more than 4 involved nodes. We conclude that receptors may reflect the degree of cytological differentiation. These results confirm that ER may be a useful guide to prognosis provided the status of the axillary nodes is known. (no Refs)

60. THE INCIDENCE OF POSITIVE OESTROGEN AND PROGESTERONE RECEPTORS IN BREAST CANCER OF GREEK WOMEN.

Vassilaros S, Adamopoulos DA, Papadiamantis J, Dessypris A, Kapolla N

Breast and Endocrine Clinic, M. Eliadi' Hosp., 2, E. Venizelou Square, Athens 601, Greece

Anticancer Res; 1(4):195-197 1981

Estrogen and progesterone receptors (ER and PR, respectively) were determined in breast tumors from 80 Greek women (23-72 yr old). Of the patients positive for both ER and PR, 15 were assayed for prolactin (PRL), thyroid stimulating hormone (TSH), and human chorionic gonadotropin (HCG beta subunit). ER assays were positive in 84.6% of premenopausal and 85.4% of postmenopausal women. PR assays were positive in 71.8% of premenopausal and 58.5% of postmenopausal women. In premenopausal women, both receptors were positive in 69.2%, ER was positive and PR negative in 15.4%, ER was negative and PR positive in 2.6%, and both were negative in 12.8%. In the postmenopausal group, 51.2% were positive for both ER and PR, 34.2% were ER positive and PR negative, and 14.6% were negative for both. The mean ratio of PR to ER concentration in the premenopausal group was 7.6 compared with 1.7 in the postmenopausal group. In receptor positive patients, PRL and TSH concentrations were similar to those of patients with cystic disease and fell within the normal range of values. HCG was not detected in any patients or controls. These data demonstrate that the frequency of positive ER and PR in Greek women with breast cancer is similar to that of other Western populations. (17 Refs)

61. HISTOLOGY AND CYTOMETRICS IN HUMAN BREAST CANCERS ASSAYED FOR THE PRESENCE OF PROLACTIN RECEPTORS.

Codegone ML, Di Carlo R, Muccioli G, Bussolati G

(c/o Bussolati), Istituto di Anatomia e Istologia Patologica, Via Santena 7, 10126 Torino, Italia

Tumori; 67(6):549-552 1981

Histology and cytometrics were evaluated in 50 cases of human breast infiltrating carcinomas (44 ductal, 6 lobular) assayed for the presence of prolactin receptors (PR). The tumors were considered PR positive when the level of specific binding reached or exceeded 0.5%. Twenty-six ductal infiltrating carcinomas and 4 lobular ones were PR positive. No strict correlation was found between PR and degree of histologic differentiation (expressed in grades) or menopausal status. Better differentiated (Grade I) ductal carcinomas were, however, mostly PR negative. Evaluation of the mean nuclear diameter (MND) and of the maximal epithelial cellularity (MEC) revealed that in ductal carcinomas a high level of PR (greater than 3% specific binding) was significantly correlated with a high MND. It is concluded that, contrary to that observed in estrogen receptor-positive tumors, PR-positive human ductal carcinomas are more likely to have large nuclei, ie, cytologically anaplastic, whereas better differentiated (Grade I) carcinomas are generally PR negative. (Author abstract) (15 Refs)

62. SIGNIFICANCE OF PROLACTIN RECEPTORS (PR) IN HUMAN BREAST CANCER. STATISTICAL ANALYSIS OF A SERIES OF 92 CASES (MEETING ABSTRACT).

Bonneterre J, Peyrat JP, Beuscart R, Cappelaere P, Demaille A

Center Oscar Lambret, Lille, France

UICC Conference on Clinical Oncology, October 28-31, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

PR were measured in breast cancer tissues from 92 patients (pts) without metastasis. Free receptors were calculated after incubation of membrane proteins with 125 I labelled human growth hormone (hGH) in the presence and absence of unlabelled ovine prolactin. Total receptors were measured by the same method after desaturation of occupied sites by incubation with 3 M $MgCl_2$ for 5 min and then cold Tris HCl (buffer pH 7.6) containing 0.1% bovine serum albumin (BSA). Tumors were consider as positive when the specific binding was higher than 0.8%. Forty-six percent of tumors were positive for free receptors and 72 percent for total receptors. PR were not significantly associated with clinical (age, wt, obesity, hormonal status, number of pregnancies, previous hormonal or antimitotic treatment) and histological (differentiation, cellular density, histoprognostic grading, stroma, number of invaded axillary nodes) features. Total RP were positively correlated to estradiol and progesterone receptors levels. Free and total RP were not correlated to 17 beta estradiol, estrone and prolactin plasma levels but pts were too few (29 pts) in this preliminary study. The desaturation with $MgCl_2$ allows to reveal the endogeneous prolactin - occupied sites and to increase the rate of positive RP. But it is too early to decide if PR levels give more information than steroid receptor for treatment and/or prognostic of human breast cancer. (no Refs)

63. IMMUNOCYTOCHEMICAL AND AUTORADIOGRAPHIC DEMONSTRATION OF PROLACTIN BINDING TO HUMAN BREAST CANCER CELLS IN TISSUE CULTURE.

Paterson JA, Salih H, Shiu RP

Dept. Anatomy, Univ. Manitoba, Winnipeg, Manitoba R3E 0W3, Canada

J Histochem Cytochem; 30(2):153-156 1982

Specific binding of human prolactin to human breast cancer cells in culture was demonstrated for the first time by immunocytochemistry and autoradiography. Using the former technique, it was found that prolactin binding to the cell surface was heterogeneous: some cells showing intense to moderate peroxidase reaction product and some cells showing absence of reaction product. After the cells were incubated with 125I-labeled prolactin and then embedded in plastic, autoradiography of sections revealed both surface-localized and intracellular silver grains, the latter suggesting internalization of prolactin. These two cytological techniques are useful for visualizing prolactin binding to human breast cancer cells and are applicable to studies on prolactin binding in human breast cancer. (Author abstract) (14 Refs)

64. THE INTER-RELATIONSHIPS BETWEEN CARCINOEMBRYONIC ANTIGEN (CEA) ESTROGEN AND PROGESTERONE RECEPTORS (ER), (PR) AND MORPHOLOGICAL CHARACTERISTICS IN HUMAN BREAST CANCER (MEETING ABSTRACT).

Sarfaty G, Nash A, Keightley D, Fisher R, Liddelow A
Prince of Wales Hospital, Randwick, New South Wales, Australia
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

We have examined the ER, PR and CEA levels in the cytosol fraction of 119 histologically confirmed cases of primary breast cancer. ER was detected in 53%, PR in 28% and CEA in 63% of the tumors. Although presence of ER correlated significantly with PR, no significant correlation was found between CEA and ER. As ER and possibly PR correlate with morphological characteristics of breast cancer, their relationship and that of CEA was examined in 32 cases where complete histological data was obtained. Tumors were graded according to the World Health Organization Classification of Scarff and Torloni. ER was found to correlate with tumor grade, higher grades of tumor having fewer receptors. Although CEA and PR were also negatively associated with tumor grade neither relationship was statistically significant. No correlation was found between tumor fibrosis, necrosis, elastosis or lymphocytes and either CEA, ER or PR. While confirming from this study that breast cancer cytosol levels of ER are significantly associated with tumor grade, no such relationship exists for CEA and PR. Elevated plasma CEA is associated with advanced breast cancer in up to 73% of cases in some studies and is a marker for advanced disease. Whether cytosol CEA is a marker of prognosis independent of ER and tumor characteristics or is a function of tumor cell number is not revealed in the present data and requires further study. (no Refs)

65. DIHYDROPTERIDINE REDUCTASE ACTIVITY IN HUMAN BREAST CANCER. STUDIES OF 382 CASES AND CORRELATIONS WITH ESTROGEN RECEPTORS (MEETING ABSTRACT).

Dhondt JL, Bonneterre J, Farriaux JP, Lefebvre J, Demaille A
Biochem Labo Free Med Fac, Lille, France
UICC Conference on Clinical Oncology, October 28-31, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Dihydropteridine-reductase (DHPR) is a NADH dependent enzyme which reduces dihydrobiopterine into tetrahydrobiopterine (THB), a cofactor of phenylalanine, tyrosine and tryptophan-hydroxylase. The study of 353 breast tumors revealed a large variation of cytosolic DHPR activities (log-normal distribution, mean: 32 nmoles/mn/mg protein). Five percent of tumors showed high values (greater than 200 nmoles/mn/mg protein), this was in discord with the previous descriptions of low DHPR activities in other cancers. Investigating 22 metastatic localizations, high DHPR was noted in 1 case, and no significant differences in activities were demonstrated when bilateral primary localizations were studied (7 cases). The significance of these high DHPR activities has not yet been estabilished; however two questions arose: 1) If DHPR, which is distributed to many tissues devoid of any of the hydroxylases requiring THB as cofactor, could also act in other metabolic processes, could DHPR activities be related to hormonal status tumors? Significant positive correlations between DHPR and estradiol receptor sites were presently established. 2) What are the relationships between Biopterin-metabolism and Folate-metabolism? Dihydrofolate-reductase activities have been considered as a marker of Methotrexate resistance.

Correlation between DHPR activities and cellular typing as metastatic potential of these tumors is presently in progress. (no Refs)

66. RAPID ANALYSIS OF ESTROGEN AND PROGESTERONE RECEPTORS USING GEL-EXCLUSION HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY.

Pavlik EJ, Von Nagell JR, Muncey M, Donaldson ES, Hanson M, Kenady D, Rees ED, Talwalkar VR
Dept. Obstetrics and Gynecology, Univ. Kentucky, Albert B. Chandler Medical Center, Lexington, KY, 40536
Biochemistry; 21(1):139-145 1982

Estrogen and progesterone receptors prepared from mouse, rat, and human uteri, as well as from human breast cancers, have been characterized by gel-exclusion high-performance liquid chromatography. The qualitative relationships previously established by sedimentation analysis between the cytoplasmic [aggregated (approx 8S), deaggregated (approx 4S), and trypsinized (approx 3.6S)] and nuclear (approx 5S) forms of the rat uterine estrogen receptor were maintained by this technique. Differences in the partition of estrogen and progesterone receptors from the same species as well as interspecies differences in these receptors were reproducibly observed. Multiple forms of human estrogen and progesterone receptors could clearly be resolved in a single analysis and were distinct from serum steroid binding tissue contaminants. Separation analyses, performed at flow rates up to 2 mL min-1, were capable of resolving all receptor forms in 10-12 min with the column returning to base line in 25 min. With this exclusion gel column (TSK-G3000SW) as a background upon which to reference different receptor forms, eight distinct partitions or elution positions have been enumerated. This approach has considerable promise for the rapid characterization of different forms of steroid-receptor proteins. Moreover, it should provide a critical advantage in minimizing the opportunities for receptor modification during separation analysis and in maximizing the opportunity to study short-lived interactions between receptors and physiologic or pharmacologic ligands. (Author abstract) (37 Refs)

67. OESTROGEN RECEPTORS IN PRIMARY BREAST CANCER: COMPARISON OF FLUORESCENT CYTOCHEMICAL AND QUANTITATIVE CYTOPLASMIC TECHNIQUES (MEETING ABSTRACT).

Furnival CM, Chong KC, Watson L, Visona A
No affiliation given
Clinical Oncology Society of Australia, November 24-17, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Two methods for the detection of estrogen receptors (ER) have been compared in 38 cases of primary breast cancer. A fluorescein-labelled estradiol (Fluoro-CEP: Zeus Scientific Inc) was used in a histochemical preparation and the results compared with a quantitative (dextran-coated charcoal) method applied to a sample of adjacent tissue. In 35 of 38 cases (92%) both methods gave a qualitatively identical result. In two cases the fluorescent method was ER-positive when the quantitative assay was negative and in the remaining case a fluorescent ER-negative sample gave a positive result on quantitative assay. Each method has its own advantages. The fluorescent method is simple and direct, but cannot be easily quantified. The dextran-coated charcoal method is complex and time-consuming but gives a quantitative result. It is concluded that where an assay result is required simply to indicate ER status, the fluorescent method described is both simple and reliable. (no Refs)

68. THE DETECTION OF GLUCOCORTICOID RECEPTORS IN BREAST CANCER BY IMMUNOCYTOCHEMICAL AND BIOCHEMICAL METHODS.

Ioannidis C, Papamichail M, Agnanti N, Garas J, Tsawdaroglou N, Sekeris CE
Hellenic Anticancer Inst., Athens, Greece
Int J Cancer; 29(2):147-152 1982

Glucocorticoid receptors have been detected in 90 human breast tumors and tumor-like conditions by the immunoperoxidase method using a specific antibody against the glucocorticoid receptor isolated from rat thymocytes. In some of the specimens the [3H]-dexamethasone binding assay was also performed and the results obtained were compared with those of the immunoperoxidase method. When the biochemical method was used, no strict correlation between the degree of binding of [3H]-dexamethasone and malignancy on the basis of histological findings could be demonstrated. In contrast, the immunoperoxidase method was in full agreement with the histological type of the tumor. Thus, nearly all malignant breast tumors (carcinomas) were positive by the immunoperoxidase method to a varying degree. Most of the examined benign tumor-like conditions (fibrocystic disease) were found to be negative. Intermediate situations, such as atypical duct or lobular hyperplasia, papillomatosis etc, were mostly positive. These findings suggest that the immunoperoxidase method, apart from its usefulness for the detection of glucocorticoid receptors in breast tissue, may be used as an early biological marker to detect early conversion of normal to hyperplastic tissue and/or malignancy of the mammary gland. (Author abstract) (14 Refs)

69. ALPHA-1-ANTITRYPSIN IN SERUM CANCER PATIENTS (MEETING ABSTRACT).

Millan Nunez-Cortes J, Senra Varela A
National Cancer Institute, Madrid, Spain
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

We have determined the alpha-1-antitrypsin (A-1-AT) concentration by radial immunodiffusion in 152 cancer patients with histological confirmation, 109 normal people and 148 non-cancer patients. This determination is useful for discerning the different groups. The mean value of A-1-AT in cancer patients (without previous treatment) was 722.55 mg % and in the normal ones was 384.50 mg/100ml. The difference with the non-cancer group was also relevant. The tumors in advanced stages (M+) have a mean value of 848.51 mg/100 ml that differs of these in local stages (T+) (587.45 mg/100 ml) and with those in loco-regional stages (N+) (650.9 mg/100 ml). The lung cancer (605.27 mg/100 ml) differs from the chronical bronchopneumopathies (380.87 mg/100 ml). The gastric cancer (873.2 mg/100 ml) differs from the gastric ulcer (468.54 mg/100 ml). The breast cancer (633.73 mg/100 ml) doesn't differ from the fibrocystic masthopathy (561.7 mg/100 ml). The alpha-1-antitrypsin behaves as a biological marker of cancer. (no Refs)

70. CYCLIC AMP-RECEPTOR PROTEINS IN HUMAN MCF-7 CELLS AND BREAST CANCER (MEETING ABSTRACT).

Eppenberger U, Almendral A, Huber P, Kung W, Handschin J

Department of Research and Gynecology, University Medical School, 4031 Basel, Switzerland

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Several recent investigations have indicated that a relationship exists between intracellular levels of cyclic (c)AMP and cAMP-dependent protein kinase isozymes type I and type II during normal and neoplastic growth and tumor regression. This study demonstrates a significant alteration in the cAMP-receptor protein pattern (regulatory subunit R-II of type II) of human neoplastic mammary tissue from surgical biopsies and human mammary MCF-7 cells as compared to normal and dysplastic mammary tissues. Photoaffinity labeling of the cAMP receptors with 8-N3-[32P] cAMP revealed on sodium dodecyl sulfate polyacrylamide gels 3 cAMP-receptor proteins of R-II (Mol wt (MW) 56,000, 54,000 and 52,000) and cAMP-receptor protein with an apparent MW of 40,000, which could not be detected in normal and dysplastic mammary cells. It is suggested that the 40,000 MW receptor results from proteolysis and has some prognostic value with respect to endocrine therapy and DBcAMP treatment of breast cancer (IND No 2025) which is under investigation. Only small amounts of the regulatory subunit R-I of isozyme type I were observed in MCF-7 cells and breast cancer tissue, whereas in normal mammary tissue no R-I could be found. (no Refs)

71. HETEROGENITY OF HUMAN TUMORS AS EVIDENCED BY DNA FLUORIMETRY (MEETING ABSTRACT).

Badaracco G, Mauro F, Modini C, Nervi C, Starace G, Tirindelli Danesi D

No affiliation given

UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Flow cytometry is a widely recognized method of rapidly assessing the proliferative status of experimental and human tumors. In our laboratory, a variety of human cancers including leukemia and non-Hodgkin lymphoma as well as solid tumors from various sites (lung, head and neck, breast, etc) have been analyzed. In agreement with a number of recent reports, important differences can be evidenced between these two classes of tumors. In particular: (1) solid tumors are generally characterized by a variable degree of aneuploidy whereas hematological tumors often exhibit normal ploidy levels; (2) the proliferative structure of solid tumors is highly heterogeneous especially with respect to the fraction of malignant cells, their distribution through the cycle phases, and the presence to a variable extent in the tumor mass of multiple cell clones; and (3) heterogenity is also typical of hematological tumors but only as far as the effect of the sampling site on the cell-age distribution is concerned. Static fluorimetry of Feulgen-stained (mitotic) single cells offers a way to confirm this kind of observation. (no Refs)

72. COMPARISON OF PHOSPHOLIPID PROFILES OF PRIMARY ADENOCARCINOMA IN THE LUNG AND OTHER ORGANS.

Itoh K, Nakamura M, Akino T
(c/o Akino) Dept. Biochemistry, Sapporo Medical Coll., Sapporo 060, Japan
Lipids; 16(12):876-880 1981

The phospholipid (PL) profile, especially content of saturated phosphatidylcholine (PC), in primary lung adenocarcinoma (ADC) was compared with that of histologically similar carcinomas from the rectum, colon, stomach, thyroid, and breast. Amounts of PL and total cholesterol were similar for the various ADC sites. Primary lung ADC contained only negligible amounts of phosphatidylglycerol, indicating that none of these ADC originated from Type II cells. The PL profile of lung ADC was similar to that of thyroid and breast ADC, but differed from those of alimentary tract ADC. Alimentary tract ADC contained significantly more phosphatidylserine. ADC of the rectum and stomach contained relatively less PC. In lung ADC, the 1-and 2-positions of PC contained 64% and 22% palmitic acid, respectively. Compared to lung ADC, the other ADC contained significantly less palmitic and stearic acids at the 1-position of PC. ADC other than lung ADC contained only 9-13% palmitic acid and had increased percentages of unsaturated fatty acids at the 2-position of PC. Compared to lung ADC, stomach ADC contained more linoleic and arachidonic acids, breast ADC more palmitoleic and oleic acids, and thyroid ADC more oleic acid. Saturated classes accounted for 20.8% of PC in lung ADC and only 6-10.7% of PC in the other ADC. Only lung ADC seemed to lack 1-alkyl or 1-alkenyl type PC. The results demonstrate marked differences between the PL profile of primary lung ADC and those of other sites. (13 Refs)

73. TUMOR STRUCTURE AND STATE OF THE ADJACENT TISSUE IN ELDERLY AND AGED PATIENTS WITH BREAST CANCER.

Ermilova VD, Korshikov SV
Dept. Pathology of Human Tumors, All-Union Cancer Res. Center, Moscow, USSR
Arkh Patol; 43(11):52-56 1981

Histological changes in mammary gland tissue were studied in 241 breast cancer patients greater than 50 yr old. The patients had been in menopause for greater than 10 yr. Infiltrating carcinoma of various degrees of malignancy was found in 81.3% of the patients. Involution of breast tissue was found in 35.6% of the patients, nonproliferating mastopathy in 29%, and proliferative mastopathy in 35.2%. Atrophy of the breast parenchyma was significantly more frequent in 60-70 and 70-80-yr-old patients (61% and 28%, respectively), than in 50-60-yr-old patients (11%). (7 Refs) (In RUS)

74. PROLACTIN AND PROLACTIN RECEPTOR INTERACTIONS IN NORMAL AND NEOPLASTIC TISSUE.

Kelly PA, Djiane J, Turcot-Lemay L
Dept. Molecular Endocrinology, Le Centre Hospitalier de l'Universite Laval, Qubec G1V 4G2, Canada
Adv Exp Med Biol; 138:211-229 1982

Regulation of hormone receptors in nitroso-methylurea (NMU)-induced mammary tumors, the interaction of prolactin with prolactin receptors, and the down-regulation of prolactin receptors induced by prolactin both in vivo and in vitro are described. Prolactin receptors in NMU-induced tumors are reduced following ovariectomy of animals with newly formed tumors (2.5 mo after NMU injection) or in those animals with tumors present for longer periods. Prolactin receptors appear to have a relatively rapid turnover, based on the rate of receptor replenishment following removal of cycloheximide. (50 Refs)

75. FLUORESCENCE-MICROSCOPIC DEMONSTRATION OF ESTROGEN- AND PROGESTERONE-RECEPTORS IN MAMMARY TUMORS OF THE DOG.

Eliing H, Staimer S
Institut fur Tierpathologie, Ludwig-Maximilians-Universitat Munchen, Veterinarstr. 13, D-8000 Munchen 22, W. Germany
Berl Muench Tieraerztl Wochenschr; 94(23):468-471 1981

Tissue sections from eight canine mammary tumors were examined by fluorescence microscope (FM) to determine estrogen- and progesterone-receptor status. Tissue samples were frozen in liquid nitrogen immediately after surgical removal. Serial sections were prepared and stained with hematoxylin and eosin, estradiol conjugate, or progesterone conjugate. Cells were graded as nonspecific, weakly, moderately, or strongly fluorescent; nuclear and cytoplasmic staining were not differentiated. Estrogen- and progesterone-conjugates accumulated in the cell cytoplasm and, to a smaller degree, in the nucleus. In each tumor examined, different areas showed different degrees of fluorescence. Fluorescence was found only in tumor cells; leukocytes, blood vessels, and adjacent connective tissue showed no fluorescence. Estrogen and progesterone receptors were found in both epithelial and myoepithelial components of tumors. Determination of receptor status by FM had the advantages over radioimmunoassay of reduced cost and equipment requirements and direct counting of fluorescent cells. Disadvantages included subjective, rather than objective grading and variation in fluorescence with the thickness of tissue sections. Results indicate that canine mammary tumors are not strictly receptor-positive or negative but consist of heterogeneous cell populations. (18 Refs) (In GER)

76. CYCLIC AMP-BINDING PROTEIN AND ESTROGEN RECEPTOR: ANTAGONISM DURING NUCLEAR TRANSLOCATION IN A HORMONE-DEPENDENT MAMMARY TUMOR.

Bodwin JS, Hirayama PH, Cho-Chung YS
Lab. Pathophysiology, NCI, NIH, Bethesda, MD, 20205
Biochem Biophys Res Commun; 103(4):1349-1355 1981

Mutual inhibition of translocations from the cytoplasm to the nucleus by estrogen receptor (ER) and cyclic AMP-binding protein was examined in a cell-free system of mammary tumors. Incubation of nuclei from hormone-dependent MTW9 rat mammary tumors with cytosol activated by 5 nano (n)M 17beta-estradiol resulted in a 4-fold increase in nuclear estrogen binding activity over the control nuclei. The presence of 100 nM cyclic AMP (cAMP) in the activated cytosol inhibited nuclear uptake of ER by 50%. Incubation of the nuclei with cytosol activated by 100 nM cAMP increased nuclear cAMP binding and cAMP-dependent protein kinase activity 4-fold. The presence of 5 nM 17beta-estradiol in the activated cytosol inhibited the nuclear cAMP binding and the protein kinase activity by 50%. No competition was found between estrogen and cAMP for each other's cytoplasmic binding proteins or the nuclear acceptor sites. Data suggest that a mutual antagonism exists between the cAMP-binding protein and ER during their nuclear translocation; the mutual antagonism was dependent on concentrations of the ligands in the activated cytosol. Activated glucocorticoid receptors did not influence the nuclear uptake of either ER or cAMP-binding proteins. Studies on the structural confirmation of cAMP- and estrogen binding proteins under controlled conditions of phosphorylation and dephosphorylation may elucidate the mechanism of antagonism between the receptors. (15 Refs)

77. DEFECTIVE BASAL LAMINA FORMATION BY TRANSFORMED MAMMARY EPITHELIAL CELLS: A REDUCED EFFECT OF COLLAGEN ON BASAL LAMINA (HEPARIN SULFATE-RICH) PROTEOGLYCAN DEGRADATION.

David G, Bernfield M
(c/o Bernfield) Dept. Pediatrics, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
J Cell Physiol; 110(1):56-62 1982

Low passage (LP, continuous basal lamina formed) and high passage (HP, scant basal lamina formed) strains of the NMuMG mouse mammary epithelial cell line were compared in terms of the nature of the 35SO4-proteoglycans accumulating and the 35S-glycosaminoglycan (GAG) turnover in cultures on collagen and plastic substrata. After 48 hr labeling on collagen, LP and HP cells had accumulated similar amounts of 35S-GAG, but HP cells had deposited less 35S-GAG on the substratum. Chasing for 48 hr revealed that the 35S-GAG produced by both lines are nearly equally stable. Sepharose CL-4B chromatography showed that the substratum-associated proteoglycan fractions, especially the basal lamina proteoglycan fraction, are deposited by the HP cells. When cultured on plastic the LP and HP monolayers accumulated similar amounts of 35S-GAG after 48 hr labeling and rapidly lost similar proportions after 24-48 hr chase. The major chromatographic proteoglycan fractions were lost from the plastic at similar rates, indicating that GAG metabolism of the two cell types does not differ on plastic. The 35S-proteoglycans accumulating in HP cultures contain more heparin sulfate and less chondroitin sulfate than those of LP cultures. Label-chase kinetic experiments showed that the reduced ability of HP cells to accumulate substratum-associated proteoglycans on collagen is due to their rapid degrading of a larger proportion of newly synthesized GAG. Experiments on plastic substrates showed that degradation rates of newly synthesized 35S-GAG are similar, and initially are more rapid than on collagen. The mechanism accounting for the inability of HP cells to respond to collagen by slowing proteoglycan degradation may involve the greater amount of heparin sulfate in HP cells or some unknown factor. (26 Refs)

78. RETINOID BINDING IN NORMAL AND NEOPLASTIC MAMMARY TISSUE.

Moon RC, Mehta RG
Life Sciences Div., IIT Res. Inst., 10 West 35th St., Chicago, IL, 60616
Adv Exp Med Biol; 138:231-249 1982

Characterization of cytosolic retinoid binding proteins and nuclear translocation of cytosolic retinoic acid binding protein (cRABP) in mammary tissue during normal and neoplastic differentiation are reported. Relatively high levels of cRABP were observed in the mammary glands from pregnant animals as well as in ovarian hormone independent tumors; in glands obtained from lactating rats and in hormone dependent tumors, lower levels of cRABP were evident. Results indicate a possible correlation between endocrine and retinoid function in both normal and neoplastic differentiation of mammary tissue. A possible selective inhibition of ovarian hormone independent tumors by the retinoids is indicated. (52 Refs)

79. BIOLOGIC MARKERS AND BREAST CANCER: A MULTIPARAMETRIC STUDY -1. INCREASED SERUM PROTEIN LEVELS.

Lamoureux G, Mandeville R, Poisson R, Legault-Poisson S, Jolicoeur R
Institut Armand-Frappier, Univ. Quebec, C.P. 100, Laval, Quebec H7V 1B7, Canada
Cancer; 49(3):502-512 1982

From early 1972 to the end of 1976, the profiles of several serum protein levels were used to monitor disease stage and prognosis of 207 patients with breast cancer. Six of these proteins, alpha 1-antitrypsin (alpha-AT), alpha 2-ceruloplasmin (Cp), beta 1-transferrin, IgA, C4, and C5, were significantly elevated in these cancer patients and were used as biologic markers in a multiparametric study. Among these breast cancer patients, 72% had at least two of these protein levels elevated, of which alpha-AT (55%), C5 (38%), and IgA (36%) levels were most commonly raised. The number of elevated proteins was parallel to disease progression as 61% (Group 1) and 74% (Group 2) of the patients with operable breast cancer and 90% of patients with metastatic disease showed an elevation of two or more of these nonspecific proteins. There was also a positive correlation between the number of elevated proteins and prognosis; of the 26 patients who died during the 5-year follow-up, only 4 (15%) had no more than one protein level elevated, and 22 (85%) had two or more protein levels elevated. On the other hand, when considered as a group, patients with no or only one protein level elevated had a better prognosis than patients with two or more levels elevated (p less than 0.03). This multiparametric study tends to indicate that the high level of these serum proteins, reflecting an abnormal biochemical profile, provides valuable information that relates to the stage of the disease and patients' prognosis. Results also suggest that these proteins may aid in differentiating the group with high recurrent risks from that with a more favorable prognosis for a given clinical and pathologic stage, illustrating their importance as biologic markers in breast cancer. (Author abstract) (58 Refs)

80. AGE, SEX CHROMATIN, AND ESTROGEN RECEPTOR STATUS IN WOMEN WITH BREAST CANCER.

Bishun NP, Smethurst M, Williams DC
Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 0TX, England
Cancer Genet Cytogenet; 4(4):353-355 1981

Results of sex chromatin (SC) counts and estrogen receptor (ER) assays in 45 breast tumors from patients less than 46 to greater than 60 yr old are presented. A trend toward higher SC frequency in patients greater than 60 yr was associated with a marked increase in the proportion of ER-positive tumors. (12 Refs)

81. MILK PROTEINS AND BREAST CANCER (MEETING ABSTRACT).

Zangerle PF, Collette J, Hendrick JC, Franchimont P
Laboratory of Radioimmunology, CHU B23, University of Leige, Leige, Belgium
Third Meeting of the French Society of Senology and Mammary Pathology, October 15-17, 1981, Versailles, France Centre Rene Huguenin; 1981

Human lactalbumin was purified from human milk; breast cyst fluid protein from breast cyst fluid. Two respective radioimmunoassays were validated. The serum lactalbumin presence is the answer of the breast to hormonal climate acting on the glandular cells, particularly prolactin. Lactalbumin levels can be correlated with a risk hormonal situation and with a risk disease such as fibrocystic disease. Lactalbumin is not a marker for breast cancer but can be a parameter of hormone dependency. Breast cyst fluid protein is not a marker of the functional activity of the breast. This protein is produced by the breast cancer. Its value is as an index of the extension of the tumor and a parameter for the follow up. The biological role of this new protein is still unknown. (no Refs)

82. ECTOPIC PRODUCTION OF PLACENTA-'SPECIFIC' TISSUE PROTEINS (PP5 AND PP11) BY MALIGNANT BREAST TUMORS.

Inaba N, Renk T, Daume E, Bohn H
(c/o Bohn) Res. Laboratories, Behringwerke AG, Postfach 1140, D-3550 Marburg (Lahn), W. Germany
Arch Gynecol; 231(1):87-90 1981

An enzyme-bridge immunoperoxidase technique was used to demonstrate the production of two placenta-'specific' tissue proteins, PP5 and PP11 in sections of the breast cancers of 16 patients. The specific antisera against human PP5 and PP11 were raised by immunizing rabbits with the purified antigens. An IgG fraction of goat antiserum against rabbit immunoglobulin was used as the second antibody. Peroxidase-rabbit antiperoxidase (PAP) complex was then applied. A slightly modified Mason PAP method was used to demonstrate the tissue antigens. Clear positive staining for PP5 was observed in 10/16 (62.5%) breast cancers, and for PP11 in 7/15 (46.7%). Positive staining was only observed in the cytoplasm. All of the specimens positive for PP11 were also positive for PP5; all six specimens negative for PP5 were also negative for PP11. Positive staining was more frequent in cells found in the periphery of the cancer mass than those in the center. No staining was observed in apparently normal breast tissues and histiocytes in the tissues and/or in the vessels. These determinations in sera might be of use in screening for breast cancer and for monitoring therapy or detecting metastases in patients with established disease. (17 Refs)

83. RADIOIMMUNOLOGICAL DETERMINATION OF TWO NEW PLACENTAL PROTEINS (PP10 AND PP12) IN PATIENTS WITH GENITAL CARCINOMA AND BREAST CANCER (MEETING ABSTRACT).

Wurz H, Luben G, Bohn H
Department of Obstet and Gynaecol, Cologne University, Marburg, W. Germany
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

PP10 and PP12 are two recently identified placental proteins which could be demonstrated in tumor tissues by an immunoglobulin enzyme-bridge technique. Specific and sensitive double-antibody radioimmunoassays have now been developed which enabled us to measure the concentrations of these proteins in body fluids and to evaluate their usefulness as potential tumor markers. Normal serum samples contained 3-10 ug/l of PP10 and 3-100 ug/l of PP12. Elevated Serum levels were found in cases of primary and recurrent breast and genital cancers. Both proteins could be detected in tumor extracts. PP10 was also elevated in some cases of benign breast disease and in patients during temporary remission. The results of serial determinations after tumorectomy and longterm controls of patients with metastatic cancer under chemotherapy will be reported. (no Refs)

84. ISOENZYMES OF LACTATE DEHYDROGENASE (LD) IN THE SERUM OF PATIENTS WITH MALIGNANT TUMOURS (MEETING ABSTRACT).

Gill PG, Thomas DW, Bais R, Huxtable R
University of Adelaide and Institute of Medical and Veterinary Science, Adelaide, Australia
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Serum LD activities are frequently abnormal in patients with malignant disease. Seventeen patients suffering from a variety of malignant tumor and were noted to have elevated serum activities of lactate dehydrogenase (LD) in the absence of other biochemical abnormalities were studied. The tumor types included teratoma of the testis (7), breast cancer (2), histiocytic lymphoma (2), melanoma (2), lung cancer (2), buccal cancer (1) and colon cancer (1). None of these patients had any evidence of cardiac, hemolytic or hepatic disorders. The patients' sera were further studied by isoenzyme electrophoresis and heat fractionation which revealed that in all 17 patients fraction LD1 and LD2 accounted for the majority of the LD present in the serum, ranging from 77 to 94 per cent of the total. The possibility that the increased activities were due to macromolecular forms of LD was excluded by sepharose gel chromatography. When possible the enzymes present in tumor tissue wer also determined. Although 3 patients had liver metasases, their serum isoenzyme patterns were different from those present in the serum other patients with liver metasases or liver damage. Eleven patients had serial determinations performed and good correlation between clinical progress and LD activities were noted. Furthermore the attainment of complete remission was associated with a return to normal LD activities and isoenzyme patterns. The presence of marked increases of LD1 and LD2 in the absence of significant cardiac, hepatic or hemolytic disease should alter one to the possibility that these isoenzymes are a product of tumor cells. They may be present despite normal total levels of LD. The occurrence of these unexpected isoenzymes in a range of common tumors in addition to the teratomas suggests they may be useful markers of tumor cell growth or death. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

85. DISEASES OF THE BREAST.

Marchant DJ
Tufts Univ. Sch. Medicine, Boston, MA
Curr Ther; 28:896-902 1981

Abnormalities of breast development, physiologic alterations, inflammations and infections, and benign and malignant changes of the breast are discussed. With respect to breast cancer, evaluation begins with an accurate and thorough history. Adjuncts to physical examination include thermography and mammography. Distinguishing between screening and diagnostic evaluation of the symptomatic patient is important. Complete evaluation of the patient with known cancer and considerations involved in surgical treatment are outlined. While optimal combinations of surgery and radiotherapy lead to recurrence in less than 5% of patients, greater than 70% will die with or as a result of active breast cancer during the 30-yr period after initial diagnosis. Significant increase in survival will depend upon earlier diagnosis prior to occurrence of metastasis or treatment of micrometastases immediately following local therapy. Estrogen-positive tumors are associated with clinical response to therapeutic hormone manipulation and to prolonged interval between diagnosis and recurrence. The relation between estrogen receptor assay of breast cancer and clinical response to cytotoxic chemotherapy remains controversial. Treatment of metastatic disease or recurrent carcinoma is discussed. (no Refs)

86. NUTRITION AND CANCER. INTRODUCTORY REMARKS.

Carroll KK
Univ. Western Ontario, Ontario, Canada
Nutr Cancer; 2(4):197-198 1981

Food consumption data, methods of food analysis, animal models, recommendations regarding cancer at specific sites (colon, breast, stomach, other sites), and data on cancer incidence and mortality have been reviewed. No dietary recommendations to the public have been made. Further experiments are needed to clarify the role of diet in carcinogenesis. (no Refs)

87. CANCER AND DIET: SLACKENING PRUDENCE.

Froissart A
No affiliation given
Vivre; (233):4-9 1981

The value of dietary moderation in cancer prevention has been observed in Mormons. Although encouraged, natural foods may also contain carcinogenic agents, such as aflatoxins. Frequent ingestion of barbecued foods is discouraged because of the hydrocarbons produced when food is braised or smoked. Without many additives, much of the food consumed would be difficult to handle or too expensive. Additives are discussed in relation to dose, use, and associated cancer risks. Colonic, prostate, and breast cancer may be related to excess fat consumption. Epidemiological, animal, and cellular studies may be used to determine the carcinogenicity of chemical agents. Dietary excess and cancer are discussed. (no Refs) (In FRE)

88. ETHYLENE DIBROMIDE (EDB). (REVISED).

NIOSH Document Development Branch
Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

Toxic and carcinogenic effects of ethylene dibromide (EDB) are reviewed. Recent experimental data has reinforced the conclusion that EDB is carcinogenic in animals and that EDB should be treated as a potential occupational carcinogen in the workplace. A ceiling limit of 0.13 ppm (1.0 mg/cubic meter) over any 15 min sampling period and use of appropriate controls to reduce worker exposure are recommended. Studies have shown a high mortality rate and a statistically significant increase in incidence of benign and malignant tumors of the spleen, mammary gland, and nasal cavity in rats exposed to EDB by inhalation at 20 ppm and fed the standard rat diet. Addition of disulfiram (0.05% by wt) to the diet resulted in an approx ten-fold increase in incidence of hepatocellular carcinomas over exposure to EDB alone. The increased interaction may not necessarily be restricted to disulfiram but may occur with similarly structured compounds such as Thiram, a fungicide and seed disinfectant. Epidemiologic studies of EDB in humans have been inconclusive because of small cohort size,

incomplete or missing exposure data, and insufficient latencies to observe carcinogenic effects. Gaseous EDB at concentrations ranging from 0.2 to 2 ppm induced significant numbers of sex-linked recessive lethal mutations in Drosophila melanogaster males. Mutation induction was directly proportional to both exposure time and exposure concentration up to 60 ppm-hr for all cell stages tested. (16 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. AN EVALUATION OF THE GENETIC TOXICITY OF EPICHLORHYDRIN. A REPORT OF AN EXPERT GROUP OF THE INTERNATIONAL COMMISSION FOR PROTECTION AGAINST ENVIRONMENTAL MUTAGENS AND CARCINOGENS.
Sram RJ, Tomatis L, Bridges BA, Clemmesen J
(c/o Lohman), Medical Biological Lab. TNO, P.O. Box 45, 2280 AA Rijswijk, The Netherlands
Mutat Res; 87(3):299-319 1981

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Robert A. Taft Lab., National Inst. Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH, 45226
Curr Intell Bull NIOSH (37): 13 pp., 1981.

3. CHEMICAL CARCINOGENESIS AND SMOKING.
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Can J Public Health; 72(6):381-385 1981

RADIATION CARCINOGENESIS

4. CELLULAR TRANSFORMATION BY RADIATION: INDUCTION, PROMOTION, AND INHIBITION.
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J Supramol Struct Cell Biochem; 16(4):311-336 1981

5. EFFECTS OF IONIZING RADIATION ON THE DEVELOPING EMBRYO AND FETUS: A REVIEW.
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Effects of Ionizing Radiation on the Developing Embryo and Fetus: A Review. Available from National Technical Information Service, Springfield, VA, as PB82-115379:, 160 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

6. BETA-CARBOLINES, PSYCHOACTIVE COMPOUNDS IN THE MAMMALIAN BODY.
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Nutr Cancer; 2(4):241-249 1981

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13. HEALTH HAZARDS OF ASBESTOS EXPOSURE.
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14. OVERVIEW OF FINNISH EPIDEMIOLOGIC STUDIES ON OCCUPATIONAL CANCER.
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Muller R, Rajewsky MF
(c/o Rajewsky) Institut fur Zellbiologie (Tumorforschung), Universitat Essen (GH), Hufelandstrasse 55, Essen 1, W. Germany
J Cancer Res Clin Oncol; 102(2):99-113 1981

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Takemura N
Dept. Public Health, Jikei Univ., 25-8, Nishi-Shimbashi 2-chome, Minato-ku, Tokyo, 105, Japan
Sangyo Igaku; 23(4):355-365 1981
In JPN

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Levine L
Dept. Biochemistry, Brandeis Univ., Waltham, MA, 02254
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Scalabrino G, Ferioli ME
Inst. General Pathology, Univ. Milan, 20133 Milan, Italy
Adv Cancer Res; 35:151-268 1981

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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PREVALENCE OF BREAST CANCER IN HUMAN POPULATIONS

1. CANCER INCIDENCE AND MORTALITY IN THE UNITED STATES, 1973-77.

Young JL, Percy CL, Asire AJ, Berg JW, Cusano MM, Gloeckler LA, Horm JW, Lourie WI, Pollack ES, Shambaugh EM
(c/o Berg) Dept. Pathology, Univ. Colorado Medical Sch., Denver, CO, 80262
Natl Cancer Inst Monogr; 57:1-187 1981

Data on cancer incidence and mortality in the United States between 1973 and 1977 are presented. Data are classified according to sex, race, age, and residence of the patients, anatomic site, and histologic type of cancer. For all areas, excluding Puerto Rico, the av annual age-adjusted incidence rates for all malignant neoplasms and for carcinoma in situ were 331.5 and 26.7 per 100,000, respectively. The most common primary sites of cancer were colon/rectum, breast, and lung, with age-adjusted incidence rates of 48.5%, 46.7%, and 46.7%, respectively. The three sites accounted for 42.7% of all malignant cancers. Seventy-eight percent of in situ lesions occurred in the female genital system. Av annual mortality due to malignant neoplasms for the total United States was 166.5. Of all cancer deaths, lung cancers accounted for 21.7%, colorectal 13.6%, and breast 9.2%. Considerable variation was noted in both incidence and mortality from cancer among various racial and ethnic groups. Generally males had higher cancer rates than females. Striking differences occured among the race-sex groups and geographic areas with respect to incidence of cancer by sites. An incidence-to-mortality ratio of 1.97 was obtained. Data is classified according to 304 specific anatomic sites. Distribution of the 8,968 non-Hodgkin's lymphomas is described in terms of anatomic site (24% were extra-nodal) and race. Of all malignant cancers, 51% were diagnosed in patients aged 65 yr and older. The median age for diagnosis of patients with malignant lesions was 65.4 yr compared with 37.1 yr for in situ lesions. Of all neoplasms, 34.7% were classified adenocarcinomas, 12.4% as squamous cell carcinomas, and 9.4% as duct adenocarcinomas. A comparison with previous data is presented. (14 Refs)

2. CANCER INCIDENCE AND MORTALITY IN METROPOLITAN DETROIT, 1973-77.

Swanson GM, Brennan MJ
Dept. Social Oncology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201
Natl Cancer Inst Monogr; 57:219-297 1981

Data on cancer incidence and mortality in metropolitan Detroit (1973-1977) are presented. Differences between data from Detroit and those obtained by the Surveillance, Epidemiology, and End Results (SEER) Program are described. Less disparity between blacks and whites occurs in incidence rates in Detroit than is seen for the total SEER population. The increase in mortality rates was greater for Detroit blacks than for blacks in all SEER areas. Cancer sites for which Detroit appears to differ considerably from the total SEER program include lung and bronchus, colon, female breast, and prostate gland. (no Refs)

3. CANCER INCIDENCE AND MORTALITY IN METROPOLITAN NEW ORLEANS, 1974-77.

Halperin ST, Wellbaecher RG, Correa P, Krementz ET
Louisiana Tumor Registry, 2-3-4 Loyola Building, Suite 1000, New Orleans, LA, 70 112
Natl Cancer Inst Monogr; 57:409-487 1981

Cancer incidence and mortality in metropolitan New Orleans (1974-77) is discussed in terms of primary site, race, sex, and age. Both malignant tumors and in situ lesions are considered. New Orleans data show an overall high cancer incidence in blacks, mainly due to excessive rates for cancer of the lung, buccal cavity, esophagus, stomach, cervix, and prostate gland. For some cancers, including breast, ovary, bladder, and kidney cancers and the lymphoma-leukemia group, whites have a moderately excessive rate compared with blacks. Differences between New Orleans data and those obtained by the Surveillance, Epidemiology, and End Results Program are described. Particularly marked is the excess of respiratory cancer in New Orleans. (no Refs)

4. CANCER INCIDENCE AND MORTALITY IN PUERTO RICO, 1973-77.

Martinez I
Dept. Health, Cancer Control Program, Box 9342, Santurce, Puerto Rico, 00908
Natl Cancer Inst Monogr; 57:947-977 1981

Data on cancer incidence and mortality in Puerto Rico (1973-77) are presented by primary site and sex. Both malignant and in situ lesions are considered. Puerto Rico had a higher incidence of cancer of the mouth, hypopharynx, esophagus, stomach, and penis in comparison with findings for all Surveillance, Epidemiology, and End Results (SEER) Program areas. The incidence for all SEER areas, excluding Puerto Rico, was higher for cancers of the lip, colon, rectum, retroperitoneum, lung, bronchus, pleura, melanoma of skin, breast, corpus uteri, ovary, testis, urinary bladder, kidney, brain, endocrine glands, and lymphomas and leukemias. (no Refs)

5. CANCER MORTALITY IN BARCELONA 1960-1978.

Bosch FX, Orta J, Garcia A, Juvanet J, Camprodon A, Pumarola A
Oncology Service, Hosp. de Sant Pau, Avda S Antonio M Claret, 167, Barcelona 25, Spain
Int J Epidemiol; 11(1):46-48 1982

Cancer mortality rates specific for sex and site for the 1960-1978 period are presented. The population covered is the municipal area of Barcelona. Rates have been adjusted taking as the standard population the Spanish census of 1970. Leading sites for males are lung, stomach and large intestine. Breast, large intestine and stomach are leading causes of death for females. Secular trends follow the general picture of the western industrial countries. (Author abstract) (3 Refs)

6. BREAST CANCER IN WOMEN AGED 30 AND UNDER.

Noyes RD, Spanos WJ, Montague ED
(c/o Spanos) Section Radiation Oncology, Loma Linda Univ. Medical Center, Loma Linda, CA, 92354
Cancer; 49(6):1302-1307 1982

Breast cancer in women 30 years of age or less accounts for 2% of all breast cancers seen today. At M D Anderson Hospital, 310 young women in this age group were seen, 141 of whom received their primary treatment there. After excluding all those with inflammatory and noninvasive carcinomas, 125 patients were analyzed for survival according to nodal status, lesion size, and pregnancy status. This group was compared to a similarly matched group of 3,380 women over age 30 yr also treated at this institution. Young women with negative nodes and those with lesions less than 5 cm in size were found to have significantly poorer survivals than older women in the same groups, in contrast to several recent reports on this subject. (Author abstract) (22 Refs)

7. CANCER IN YOUNG ADULTS (AGES 15 TO 34).

Silverberg E
Dept. Epidemiology and Statistics, American Cancer Society, New York, NY
CA; 32(1):32-42 1982

Cancer is the leading disease killer of young adults between the ages of 15 and 34. In the United States cancer deaths among young men are exceeded only by accidents, suicide, and homicide, and among young women only by accidents. Statistical data are presented for mortality in 1978 resulting from disease at the five leading cancer sites for both males and females, by 4-yr intervals. Annual death rate trends since 1950 are given for the leading sites: leukemia, Hodgkin's disease, brain, testis, and non-Hodgkin's lymphoma (male) and uterus, leukemia, breast, brain, and Hodgkin's disease (female). Data on cancer incidence from the NCI's Surveillance, Epidemiology, and End Results Program covering 1973-1978 are also presented. Survival rates and treatment modalities for 18 sites are summarized in tables. Highlights of the data are indicated for the leading cancer sites in young adults: leukemia, breast, brain and nervous system, testis, Hodgkin's disease, non-Hodgkin's lymphoma, uterus, thyroid gland, and skin. (no Refs)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

8. THE EPIDEMIOLOGY OF BREAST CANCER AS IT RELATES TO MENARCHE, PREGNANCY, AND MENOPAUSE.

Pike MC, Henderson BE, Casagrande JT, Segaloff, Petrakis
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep; 8:3-19 1981

Epidemiology of breast cacer (BC) was reviewed in Japan. The following factors were included: international variation, secular trends, key risk factors, relationship between age and the incidence of epithelial tumors, the age incidence of BC, predictive relative risks for menarche, first full-term pregnancy (FFTP) and menopause, and predicted BC incidence. An early menarche, late age at FFTP, and late age at menopause all increase the risk of BC. The factors were brought together into a mathematical model assuming different rates of metabolism. Observed relative risks associated with different ages at menopause were overestimated. It was concluded that a more involved estimation parameter is needed. (31 Refs)

9. INCREASED AVAILABILITY OF SERUM ESTROGENS IN BREAST CANCER: A NEW HYPOTHESIS.

Siiteri PK, Hammond GL, Nisker JA, Korenman SG, Topp, Bulbrook RD, Henderson BE, Welsch, Meites, Rosen, Lippman, Sirbascu, Petrakis
Reproductive Endocrinology Center, Univ. California, San Francisco, CA, 94143
Banbury Rep; 8:87-106 1981

Mechanism whereby obesity appears to increase the impact of estrogens on target tissue was studied. Measurements of the percentage of free steroids in serum that closely approximates physiologic conditions indicated that estradiol binding to sex-hormone-binding globulin is of potential physiologic importance. Obesity increases target tissue exposure to estrogen, and chronic stimulation of the breast epithelium over a sufficient period of time, may lead to benign breast disease, and set the stage for cancer in those women who are exposed to an effective dose of virus, irradiation, or carcinogens. (58 Refs)

10. POSSIBLE RELATED RISKS TO BREASTFEEDING.

Senie RT
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, 60 College St., New Haven, CT, 06510
JOGN Nurs; 11(1):34-36 1982

The possible relationship between breastfeeding and mammary cancer is discussed. Studies have shown that increasing parity is inversely related to the risk of developing breast cancer, regardless of breastfeeding history. Primigravida patients over the age of 30 are at greater risk of breast cancer than younger primigravida. Women with a first degree family history who developed breast malignancies were approx 11 yr younger at diagnosis than women with no family history. Transmission of a mammary agent from mother to offspring through breast milk has been observed in mice; foster-feeding resulted in a lower incidence and later age of mammary tumor development. If such a transmitted factor functions in humans, the age of diagnosis of a breast tumor would be expected to be lower in breastfed daughters of women who developed breast cancer. No conclusive patterns have been observed in humans. Pregnant women considering breastfeeding should be made aware of the potential risk of transmission of a viral agent to their offspring. Breast-fed daughters may be at increased risk of developing cancer and breast-fed sons may obtain the viral agent and later transmit it to his offspring in the seminal fluid. (29 Refs)

11. BREAST CANCER AND ALCOHOLIC-BEVERAGE CONSUMPTION.

Rosenberg L, Shapiro S, Slone D, Kaufman DW, Helmrich SP, Miettinen OS, Stolley PD, Levy M, Rosenshein NB, Schottenfeld D, Engle RL
Drug Epidemiology Unit, Boston Univ. Sch. Medicine, 777 Concord Ave., Cambridge, MA, 02138
Lancet; 1(8266):267-271 1982

The relation between breast cancer and alcoholic-beverage consumption was evaluated in a case-control study of 1,152 women with breast cancer and two groups of control women - 519 with endometrial or ovarian cancer, and 2,702 with non-malignant disorders. The relative-risk estimate of breast cancer, with allowance for all potential distorting factors, for women who had ever drunk alcoholic beverages relative to those who had never drunk was 1.4 (95% confidence interval, 1.0-2.0) when the comparison group was the group with endometrial or ovarian cancer and 1.9 (1.5-2.4) when the controls who had non-malignant disorders were the comparison group. the association was evident for beer, wine, and spirits. The association was not explained by any of the major known risk factors for breast cancer, but we had no information on dietary factors. The findings support the hypothesis that alcohol consumption, or related dietary factors, increases the risk of breast cancer. (Author abstract) (20 Refs)

12. BILATERAL CARCINOMA OF THE BREAST: EPIDEMIOLOGY AND HISTOPATHOLOGY.

Adami HO, Hansen J, Jung B, Lindgren A, Rimsten A
(c/o Hansen) Dept. Oncology, Univ. Hosp., S-750 14 Uppsala, Sweden
Acta Radiol Oncol Radiat Phys Biol; 20(5):305-309 1981

A history of previous carcinoma in the contralateral breast was found in 66 of 1,351 women (5%) consecutively diagnosed as having breast carcinoma. The mean time interval between the diagnosis of the first and second tumor was 10.0 yr (range 0-37 yr); 63 of the tumors were metachronous. No significant differences were found between the first and the second carcinoma with respect to the Ackerman malignancy grading or the frequency of axillary node involvement. High risk groups for bilateral disease could not be defined on the basis of information about familial occurrence, parity, age at first birth, or malignancy grade. (Author abstract) (26 Refs)

13. COFFEE, TEA AND CANCER: HOW TO TEST HYPOTHESES ON LIFESTYLE AND DISEASE?.

Olsson H, Brandt L
Onkologiska kliniken, Lund, Sweden
Lakartidningen; 79(4):196-197 1982

Coffee and tea consumption of 550 tumor patients was analyzed based on questionnaire data. The patients included 19 with seminomas, 36 with cancer of the upper part of the digestive tract (lips, oral cavity, epipharynx, hypopharynx and esophagus), 59 with Hodgkin's disease, 64 with tumors of the larynx and lungs, 36 with thyroid tumors, 120 with cancer of the urinary bladder or kidneys, 28 with skin cancer, 94 with breast cancer, 16 with testicular teratomas, 28 with melanomas, 20 with cancer of the lower parts of the digestive tract (stomach, bile ducts, pancreas, colon and rectum), and 18 with tumors of the paranasal sinuses, auditory meatus and parotid glands. The median coffee consumption of the patients was 3-5 cups/day, ie, approx the same as in the general population. Fifty-three per cent of the patients with seminomas, 50% of those with cancer of the upper part of the digestive tract and 47% of those with Hodgkin's disease consumed large amounts of coffee (5 cups/day or more). The median tea consumption of the patients was 0 cup/day. Forty-four per cent of the patients with testicular teratomas, 31% of those with thyroid tumors, 32% of those with seminomas, and 29% of those with Hodgkin's disease consumed large amounts of tea (2 cups/day or more). The findings indicate that hypotheses based on complex data on lifestyle (education, occupational status, living conditions, dietary and smoking habits, and alcohol consumption) should be tested in epidemiological studies, rather than the possible relationship between tea and coffee consumption, on one hand, and certain diseases, on the other hand. (6 Refs) (In SWE)

14. MAMMARY CANCER DURING PREGNANCY.

Prodan I, Letica D, Majerovic M
Klinicki bolnicki centar - Kirurska klinika, Medicinski Fakultet u Zagrebu, Zagreb, Yugoslavia
Libri Oncol; 10(2/3):143-145 1981

Incidence of mammary cancer (MC) associated with pregnancy (PR) is around 3%. PR does not seem to influence MC. Prophylactic interruption of PR and spaying do not increase the possibility of MC cure. PR does not prevent relapse. MC associated with PR is curable. (14 Refs) (In SCR)

15. HORMONE PROFILES IN YOUNG WOMEN AT RISK OF BREAST CACER: A STUDY OF OVARIAN FUNCTION DURING THEELARCHE, MENARCHE, AND MENOPAUSE AND AFTER CHILDBIRTH.

Brown JB, Siiteri, Pike MC, Henderson BE

Dept. Obstetrics and Gynecology, Univ. Melbourne, Parkville, Victoria, 3052, Australia

Banbury Rep; 8:33-56 1981

Ovarian functions of women at various stages of their reproductive life were studied to find out more about the role of hormonal changes as a risk factor in breast cancer. Results of the study of the normal ovulatory cycle, anovulatory cycles, absent ovarian activity, values found in children, longitudinal studies over menarche, returning fertility after childbirth, and waning ovarian activity at the menopause are presented. It was indicated that during normal ovulatory cycle, increased estrogen values in the absence of raised progesterone values occur for an av of 5 days only. Two types of anovulatory cycles can be identified: no human yet has been encountered who does not excrete estrogens in the urine as measured by methods of sufficiently high sensitivity, and anovulatory cycles that are much more common in teenage girls, after childbirth, and during the approach to menopause. (7 Refs)

16. BREAST CANCER: DIET AND HORMONE METABOLISM.

Hill P, Garbaczewski L, Kasumi F, Kuno K, Helman P, Wynder EL, Topp W, Pike MC, Henderson BE, Segaloff A, Sirbasku DA, Korenman SG, Cole P, Zumoff B

Naylor Dana Inst. Disease Prevention, American Health Foundation, Valhalla, NY, 10595

Banbury Rep; 8:257-277 1981

The effect of diet modification on hormonal metabolism of women at low risk (bla ck South African and Japanese) and women at high risk (North American caucasian) for breast cancer was investigated. Differences in the hormonal profile during the menstrual cycle between the three races of women were noted. Differences in pituitary response in circulating hormone levels and in duration of menstrual cycle occurred when a Western diet was interchanged for a vegetarian diet, and vice versa. The therapeutic value of this observation is unknown. (94 Refs)

17. BODY SIZE AND BREAST CANCER RISK.

de Waard F, Pike MC, Meites J

Dept. Epidemiology, Univ. Utrecht, Inst. Social Medicine, Utrecht, The Netherlands

Banbury Rep; 8:21-30 1981

Effects of wt and height on breast cancer risk was investigated in 258 cases. Risk of estrogen receptor positive (ER) breast cancer increased with increasing wt, and the risk of an ER- breast cancer decreased with increasing wt. Late age at menopause is associated with obesity; this effect may be mediated by an extraovarian surplus of estrogen. (35 Refs)

18. ESTROGEN RECEPTOR ASSAYS IN FAMILIAL AND NONFAMILIAL BREAST CANCER.

Ottman R, Hoffman PG, Siiteri PK, Korenman SG
G. H. Sergievsky Center, Faculty Medicine, Columbia Univ., 630 West 168th St., New York, NY, 10032
Banbury Rep; 8:197-211 1981

Familial and nonfamilial breast cancer was compared with respect to the binding capacity (ER) and dissociation constant (KD) of the estrogen receptor. ER content of breast cancer tissue was influenced by the hormonal environment in which the tumor had grown and by tumor pathology. Elevated KD values observed in familial breast cancer may reflect an underlying endocrine abnormality which resulted in the development of breast cancer. Tissue estrogen concentrations may be higher in familial than nonfamilial breast cancer, and some of the variation in ER and KD may be explained by genetically determined differences in endocrine factors that relate to susceptibility to breast cancer. (12 Refs)

19. A PROSPECTIVE STUDY OF THE RELATION BETWEEN THYROID FUNCTION AND SUBSEQUENT BREAST CANCER.

Bulbrook RD, Thomas BS, Fantl VE, Hayward JL, Lippman M, Siiteri PK, Korenman SG
Dept. Clinical Endocrinology, Imperial Cancer Res. Fund, London WC2A 3PX, England
Banbury Rep; 8:131-141 1981

Prospective studies of 5,000 normal women were conducted to investigate the relationship between thyroid function and the development of breast cancer. Up to the age of 45 yr, thyroid dysfunction was not correlated to increased risk by women with a positive family history of breast cancer and was of no etiologic significance in the precancer group. In peri- and postmenopausal women with hypothyroidism, the thyroid gland appears to be involved in the development of breast cancer. (18 Refs)

20. EPIDEMIOLOGIC STUDIES OF MUTAGENICITY OF BREAST FLUIDS - RELEVANCE TO BREAST CAN CER RISK.

Petrakis NL, Pike MC, Korenman SG
Dept. Epidemiology and International Health, Univ. California, San Francisco, CA, 94143
Banbury Rep; 8:243-255 1981

Secretion and accumulation of certain chemical substances by the breast might result in initiation and promotion of benign and malignant breast disease. Breast fluid collected from 456 women was tested for mutagenic activity with the Ames Salmonella mutagenicity test. Putative mutagenic substances were present in the breast fluids of 6.7% of the women. High concentrations of hormones have been found in breast aspirates which could act as promoting factors. Preliminary data on cerumen type and cytologic dysplasia suggested that a genetic factor affecting breast secretion may indirectly influence exposure of breast epithelia to carcinogens. (32 Refs)

21. FECAL STEROID METABOLITES AND BREAST CANCER RISK.

Papatestas AE, Panvelliwalla D, Tartter PI, Miller S, Pertsemlidis D, Aufses AH
Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY, 10029
Cancer; 49(6):1201-1205 1982

Women with breast cancer (n = 78) had a higher excretion of total fecal steroids in mg/gm of dry weight (56 37) compared to controls (45 -29; n = 71) (p = 0.03). Increases in both total neutral steroids and total bile acids in cases contributed to this significant difference. Lean women (Quetelet's index less than 3.5) with breast cancer seemed to have inappropriately high excretion of total fecal steroids (56 -35), which was significantly higher than that of controls (41 -27) (p = 0.03). Obesity resulted in higher excretion of fecal steroids only in controls. The differences persisted, even after pairing control cases for race-ethnicity and menopausal status. In 59 such pairs, cases had higher values (56 -33), compared to controls (41 -26) (p = 0.008). Significant differences (p = 0.005) were also present in 24 post-menopausal pairs, while in 35 pre-menopausal pairs a similar trend, but no significant differences were noted. Women with benign breast disease had higher total fecal steroids (51 -34) compared to the other controls (38 -21) (p = 0.05). This observation suggests a common etiology between benign breast disease and breast cancer. There were no significant differences in dietary intake of total calories, total fat or dietary cholesterol between controls and cases suggesting that the observed differences in fecal steroids could be attributed to higher endogenous synthesis of cholesterol in cases. (Author abstract) (23 Refs)

22. LEGAL ABORTION: THE PUBLIC HEALTH RECORD.

Cates W
Venereal Disease Control Div., Center for Prevention Services, Centers for Disease Control, Atlanta, GA, 30333
Science; 215(4540):1586-1590 1982

The increasing availability and utilization of legal abortion in the United Stat es had several important effects on public health in the 1970's. It reduced deaths and surgical complications among women of childbearing age, it made possible the development of safer surgical procedures for pregnancy termination; and it increased the provision of low-cost outpatient gynecologic services. There is some concern about potential adverse outcomes in future desired pregnancies and possibly higher risks of breast cancer in certain women. (Author abstract) (97 Refs)

23. ALCOHOL AND CANCER.

MacSween RN
Univ. Dept. Pathology, Western Infirmary, Glasgow, Scotland
Br Med Bull; 38(1):31-33 1982

Epidemiologic and experimental studies are reviewed. Heavy alcohol consumption is assessed as a prime carcinogen of the esophagus and the mouth, a contributor of some type to carcinogenesis of the pharynx and larynx, and a cause of primary hepatocellular carcinoma in conjunction with hepatic cirrhosis. Associations with cancer of other portions of the gastrointestinal tract, the breast, thyroid, kidney, and bladder are equivocal. The actual mode of action is not known; possibilities are discussed. (30 Refs)

24. MORTALITY AMONG PVC-FABRICATING EMPLOYEES.

Chiazze L, Ference LD
Div. Biostatistics and Epidemiology, Georgetown Univ. Sch. Medicine, 3750 Reservoir Road, N. W., Washington, DC, 20007
Environ Health Perspect; 41:137-143 1981

Causes of deaths among 3,847 white active and retired workers in 17 plants producing polyvinyl chloride (PVC) which occurred during the period 1964-1973 were studied. Proportionate mortality ratios (PMR) were calculated for various causes and compared with two standards: (1) the age-, sex-, and cause-specific mortality ratio for whites in 1968 and (2) mortality rates for the individual years 1964-1973. When compared with the 1968 standard, PMR for white males were significantly increased for the categories 'all cancers,' 'digestive cancers,' 'respiratory cancers,' and 'other and unspecified cancers.' PMR for white females were significantly increased for the categories 'all cancers,' 'digestive cancers,' 'breast cancer,' 'urinary cancer,' and 'other and unspecified cancers.' When compared with standards for individual years, results were consistent with those for the 1968 standard but PMR were generally lower. Case-control analysis of 44 deaths due to breast cancer suggested an increased risk among PVC workers; the actual increase was not significant, possibly due to sample size. Analysis of sampling methods indicated that the study was capable of detecting only large increases in risk. (14 Refs)

25. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.

Tarka SM
Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

Toxicology of cocoa and methylxanthines (caffeine, theobromine, and theophylline) was discussed with respect to the following: physical properties; toxic effects of cocoa and theobromine in the diets of various animals; biological effectiveness of the methylxanthines in cocoa; toxicity of methylxanthines; distribution, metabolism, and excretion in animals and humans (metabolism during pregnancy, lactation, and growth; diet and drug influence on methylxanthine metabolism); pharmacological properties of the methylxanthines; effects of methylxanthines on growth and other physiological processes; effects on reproduction; teratogenesis; mutagenesis; chronic toxicity/carcinogenesis; SCOGS report; and fibrocystic breast disease. Research on teratogenic and mutagenic effects of caffeine was thought to be relatively abundant, but there are only a few reports on the carcinogenic effects of caffeine and none on such effects of cocoa powder, theobromine, theophylline, or tea. (203 Refs)

POSSIBLE IATROGENIC FACTORS IN HUMAN BREAST CARCINOGENESIS

26. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.

Keisey JL, Bulbrook RD, Korenman SG, Silteri PK, Henderson BE
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Banbury Rep; 8:215-228 1981

Epidemiological studies of the relationship between use of oral contraceptives (OC) and estrogen replacement therapy to the development of breast cancer are reviewed. No major study of OC has demonstrated a positive or negative overall association. With at least a 15-yr latent period, current studies will better evaluate the association between OC and breast cancer. Studies on estrogen replacement have provided conflicting results; no firm conclusion has been made. (48 Refs)

27. EXOGENOUS ESTROGENS: A CONTINUING CONTROVERSY.

Malkasian GD
Dept. Obstetrics and Gynecology, Mayo Clinic, 200 First St., SW, Rochester, MN, 55901
Geriatrics; 37(3):79-81,85-86,88 1982

The possible connection between exogenous estrogen (EE) and myocardial infarction (MI) and endometrial (EC) and breast cancer (BC), which are leading causes of death in older women is discussed. In a prospective study, EC patients and matched controls were evaluated for estrone and estradiol; no significant difference in the two groups was noted. Although multiple objections have been raised to current studies of EE and EC, a chronologic survey of the literature appears to yield consistent results with clear clinical implications. Cited data collectively and consistently show the woman who is a long term estrogen user to be at increased risk for EC, at no increased risk for MI, and at no increased risk for BC. Precise indications for the use of EE have to be determined. The potential user has to be evaluated, the risks disc used, and a monitoring program set up which the patient must follow strictly. Evaluation should include a complete history and physical, with precise attention to wt, blood pressure, breast, bone, and vaginal epithelial condition, Papanicolaou smear, and uterine size. The history should take note of parity, tendency to fluid retention, previous cardiac failure, BC or EC, deep thrombophlebitis, and presence or absence of uterus. The estrogen chosen should be the smallest amount that might control the symptoms of menopause, used in a cyclic manner and for a short duration. A follow-up annual physical examination is necessary, plus immediate endometrial sampling on any reported uterine bleeding, or breast biopsy for palpable mass. (26 Refs)

28. DIAZEPAM AND THE RISK OF BREAST CANCER.

Kaufman DW, Slone D, Shapiro S, Rosenberg L, Helmrich SP, Miettinen OS, Stolley PD, Levy M, Schottenfeld D
Drug Epidemiology Unit, Boston Univ. Sch. Medicine, 777 Concord Ave., Cambridge, MA, 02138
Lancet; 1(8271):537-539 1982

The relation of breast cancer to diazepam use was evaluated in a case-control study of 1,236 women with breast cancer and 728 control subjects with other malignancies. Compared to women who never used diazepam, the relative risk for women who used the drug at least 4 days per wk for at least 6 mo was estimated to be 0.9, with 95% confidence limits of 0.5 and 1.6. There was no apparent association for recent use, or for use in the distant past, although confidence intervals were fairly wide in these categories. The results were not explained by various potential confounding factors, including the major risk factors for breast cancer. The findings suggest that regular diazepam use does not increase the risk of breast cancer relative to other cancers. (Author abstract) (11 Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

29. SITE-SELECTIVE GROWTH OF A HORMONE-RESPONSIVE HUMAN BREAST CARCINOMA IN ATHYMIC MICE.

White AC, Levy JA, McGrath CM

Dept. Tumor Biology, Michigan Cancer Foundation, Detroit, MI, 48201

Cancer Res; 42(3):906-912 1982

MCF-7 is a human breast cancer line which requires estradiol supplementation for growth in sc tissues of athymic mice. In order to evaluate the influence of host site on hormone-dependent tumorigenicity and growth, MCF-7 cells were inoculated into tissues varying in ability to concentrate exogenous estradiol. Tumorigenicity was defined in terms of latency, threshold inoculum size, and tumor growth and progression. We observed that sites such as lung rarely supported MCF-7 tumors. However, moderately estrophilic sites such as mammary fat and adjacent subcutaneum and dermis supported the growth of small MCF-7 tumors from large tumor cell inocula, but only in estrogenized mice. In contrast, the highly estrophilic sites, brain and periuterine tissues, produced rapidly growing tumors from small cell inocula. Only in periuterine tissues did tumors develop in the absence of exogenous estradiol. These studies demonstrate that tumorigenicity and growth rates of estrogen-dependent MCF-7 tumors vary as a function of tissue implantation site. (Author abstract) (46 Refs)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

30. MAMMARY TUMORS INDUCED BY COMBINED TREATMENT WITH NITROSOUREA AND SEX HORMONES.

Ird EA, Smirnova IO

Center for Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR

Vopr Onkol; 27(12):43-46 1981

Transplacental treatment with sinestrol and testosterone-propionate reduces the incidence of spontaneous benign mammary tumors in rats. Treatment of immature female rats with nitrosoethylurea is followed by an earlier development of mammary fibroadenomas. A combined treatment with testosterone-propionate and nitrosoethylurea increases the incidence of mammary fibroadenoma and decreases its mean latent period. Fibroadenoma induction is accelerated by treating adult rats with nitrosoethylurea alone, while combined treatment induces primary mammary tumors at an earlier stage. The morphology of tumors induced by different schemes of combined treatment remains identical. (Author abstract) (8 Refs) (In RUS)

31. 2-BROMO-ALPHA-ERGOCRYPTINE (CB-154) AND TAMOXIFEN (ICI 46,474) INDUCED SUPPRESSION OF THE GENESIS OF MAMMARY CARCINOMAS IN FEMALE RATS TREATED WITH 7,12-DIMETHYLBENZANTHRACENE (DMBA): A COMPARISON.

Welsch CW, Goodrich-Smith M, Brown CK, Mackie D, Johnson D

Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824

Oncology; 39(2):88-92 1982

Daily treatment of female Sprague-Dawley rats with 2-bromo-alpha-ergocryptine (CB-154) (prolactin suppressor) or Tamoxifen (estrogen antagonist) for 33 days before and after 7,12-dimethylbenzanthracene (DMBA) administration reduced (p less than 0.05) the incidence of mammary carcinomas by 58 and 49%, respectively. A combination of CB-154 and Tamoxifen further reduced (p less than 0.05) mammary carcinoma incidence by an additional 50-59%. Treatment with Tamoxifen for 66 days beginning 33 days after carcinogen treatment reduced (p less than 0.05) the incidence of mammary carcinomas by 65%; CB-154 treatment, during the same time period, did not significantly effect the final yield of mammary carcinomas. Th combination of Tamoxifen and CB-154 was comparable to Tamoxifen alone in suppressing the incidence of mammary carcinomas in the latter study. These results demonstrate a substantial suppressive and synergistic effect of Tamoxifen and CB-154 in the initiating phases of mammary carcinogenesis while in the early promoting phases of this oncogenic process, short-term treatment with Tamoxifen was superior to CB-154 treatment; no synergism between these clinically important compounds was observed. (Author abstract) (27 Refs)

32. CORRELATION BETWEEN RETINOID INHIBITION OF N-METHYL-N-NITROSOUREA-INDUCED MAMMARY CARCINOGENESIS AND LEVELS OF RETINOIC ACID BINDING PROTEINS.

Mehta RG, McCormick DL, Cerny WL, Moon RC

Lab. Pathophysiology, Life Science Div., IIT Res. Inst., 10 West 35th St., Chicago, IL, 60616

Carcinogenesis; 3(1):89-91 1982

A correlation was made between the ability of retinoids to suppress N-methyl-N-nitrosourea (MNU)-induced mammary carcinogenesis and the levels of cytosolic retinoic acid binding proteins (cRABP) in the cytosol of MNU-induced mammary tumors. Although retinyl acetate and N-(4-hydroxyphenyl)retinamide were found to be effective inhibitors of mammary carcinogenesis in intact hosts, both retinoids were significantly more active in ovariectomized rats than in intact animals. Quantitative analyses of cRABP in the tumors indicated that mammary cancers arising in animals which were ovariectomized 1 wk after MNU administration contained significantly increased concentrations of cRABP compared to cancers appearing in intact rats. In addition, when animals bearing palpable mammary tumors were ovariectomized, the tumors which continued to grow contained significantly higher levels of cRABP than did tumors which stopped growing or regressed. These data suggest that the selective inhibition of ovarian hormone-independent mammary cancer by retinyl acetate and N-(4-hydroxyphenyl)retinamide may be mediated through an increased level of cRABP in tumor cells of ovariectomized hosts. (Author abstract) (21 Refs)

33. EFFECT OF RETINYL ACETATE ON THE OCCURRENCE OF OVARIAN HORMONE-RESPONSIVE AND -NONRESPONSIVE MAMMARY CANCERS IN THE RAT.

Thompson HJ, Meeker LD, Tagliaferro AR, Becci PJ
Dept. Home Economics, Univ. New Hampshire, Pettee Hall, Durham, NH, 03824
Cancer Res; 42(3):903-905 1982

The inhibitory activity of retinyl acetate against the induction of ovarian hormone-responsive and -nonresponsive mammary gland adenocarcinomas was studied in intact and castrated female Sprague-Dawley rats. Three experiments were conducted. Mammary cancer was induced by a single po administration of 7,12-dimethylbenz(a)anthracene (DMBA) at 50 days of age. Animals in Experiments 1 and 2 each received 20 mg DMBA, whereas those in Experiment 3 received 15 mg. In all experiments, animals were fed a chow diet supplemented per kg with either a placebo or 328 mg retinyl acetate starting 7 days after carcinogen treatment. In Experiment 1, rats were castrated at either 7, 60, or 90 days postcarcinogen and were killed 120 days after DMBA was given. In Experiment 2, rats were castrated 30 days after DMBA and were killed 240 days after carcinogen treatment. In Experiment 3, rats were castrated when a detected tumor attained a measurable diameter, and the hormone responsiveness of their tumors was subsequently determined. The experiment was terminated 279 days after DMBA treatment. In both intact and castrated rats, mammary tumor occurrence was inhibited by treatment with retinyl acetate. However, there were no differences in the latency to appearance time of hormone-responsive and -nonresponsive cancers in intact animals receiving either placebo or retinyl acetate. The data indicate that retinyl acetate inhibits DMBA-induced mammary tumorigenesis in either the presence or the absence of the ovaries. It appears that retinyl acetate is effective in inhibiting both ovarian hormone-responsive and -nonresponsive mammary tumors. (Author abstract) (15 Refs)

34. INTERACTION OF DIETARY FAT AND THE THYMUS IN THE INDUCTION OF MAMMARY TUMORS BY 7,12-DIMETHYLBENZ(A)ANTHRACENE.

Wagner DA, Naylor PH, Kim U, Shea W, Ip C, Ip MM
(c/o M. Ip) Dept. Experimental Therapeutics, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Cancer Res; 42(4):1266-1273 1982

The interaction of dietary fat and the thymus in the induction of mammary tumors by dimethylbenz(a)anthracene has been examined in female Sprague-Dawley rats. In these experiments, rats fed diets of 0.5% (low fat), 5% (normal fat), or 20% (high fat) corn oil from weaning (21 days of age) were thymectomized or sham thymectomized at 35 days of age and were given 5 mg of dimethylbenz(a)anthracene at 55 days of age. Thymectomy exerted a protective effect in rats fed low and normal fat diets, and this was not reversed by Thymosin Fraction V. In high fat-fed rats, tumorigenesis was increased compared to the low fat groups, and in addition, the protective effect of thymectomy was absent. This differential effect of thymectomy could not be explained on the basis of changes in prolactin concentration, since prolactin levels were decreased in all dietary groups. Neither diet nor thymectomy affected corticosterone levels or the estrus cycle of mature rats. Peripheral blood lymphocytes were, however, decreased by both thymectomy and increasing the fat content of the diet. It is hypothesized that the promoting effect of dietary fat on dimethylbenz(a)anthracene-induced mammary tumorigenesis is mediated via the immune system, although a role for the endocrine system still cannot be ruled out. (Author abstract) (66 Refs)

35. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.

Meites J, Aylsworth CF
Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:365-376 1981

Effects of neuroleptic drugs (ND) on secretion of anterior pituitary and target gland hormones, mechanisms by which ND influence anterior pituitary function, and effects of ND on development and growth of mammary tumors (MT) in murine species and in human subjects are reviewed. ND stimulate prolactin and inhibit gonadotropin secretion in animals and humans. Administration of ND can profoundly affect MT in rats and mice. A definite role for prolactin in MT development and growth has not been demonstrated, but estrogen has been shown to be of primary importance in humans. (71 Refs)

36. STIMULATION OF S-9 FRACTION METABOLISM IN RAT LIVER AND BREAST BY VITAL DYES.

Silva MH, Lee RE, Petrakis NL
Dept. Epidemiology and International Health, Univ. California, San Francisco, CA, 94143
Toxicol Lett; 10(2/3):205-208 1982

Known mutagens metabolized in rat liver and breast supernatant fractions were used in the Ames test to assess metabolizing enzyme induction by vital dyes. The mutagen 2-aminoanthracene (2AA) showed a 70% activity increase with neutral red, an 89% increase with methylene blue, and a 49% increase with trypan blue in treated rat liver fractions. The lowest and greatest increase in mutagenic activity with liver fractions was seen with 6-aminochrysene and diaminofluorene, respectively. An activity increase in treated breast fractions was found only with 2AA. Liver tissue was more readily induced than mammary glands of midpregnant rats. (11 Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

37. STUDIES OF OESTROGEN METABOLISM IN POSTMENOPAUSAL WOMEN WITH CANCER.

James VH, Reed MJ, Folkerd EJ
Dept. Chemical Pathology, St. Mary's Hosp. Medical Sch., London W2 1PG, England
J Steroid Biochem; 15:235-246 1981

Metabolic clearance rates (MCR) and production rates (PR) for estrone (E1) and estradiol (E2) were measured in six menopausal women with endometrial cancer (EC), five with endometrial hyperplasia, and two normal women; plasma concentrations (PC) of E1 and E2 were measured in postmenopausal women with breast cancer (BC). Significant correlation was found between MCR-E1 and percent ideal body weight. In spite of the elevated MCR of E2 seen for women with EC, the normal or low PC of E2 found for these women resulted in values for the PR of E2 that were mainly similar to the range reported for normal menopausal women. In most subjects E1 accounted for less than 40% of the E2 produced. Results suggest that E1 is not the only precursor and source of E2 in postmenopausal women. Binding capacity of sex hormone binding globulin (SHBG) expressed as ug dihydrotestosterone/100 ml plasma, was similar in women with BC (2.2 -1.3), benign breast disease (1.9 -1.0), and normal women (2.5 -1.8). This supports the observation that in some BC patients the unbound E2 fraction is elevated by a mechanism other than reduced SHBG concentration. Range of conversion of androstenedione to E1 in normal adipose tissue samples was substantial, varying from 0.5-44.0 picog E1/mg protein/3 hr, indicating that the more efficient conversion reported from in vivo studies in heavier women is not due to more efficient aromatization in adipose tissue in these women, and may therefore reflect only the large amount of tissue available. Adipose tissues examined converted E1 to E2 under the experimental conditions employed demonstrating the tissue as a potentially important site of 17beta-hydroxysteroid dehydrogenase activity, and thus of E2 production. (54 Refs)

38. STEROID HORMONE CONTENT OF BREAST TISSUE IN PATIENTS WITH MAMMARY TUMORS.

Vallent K, Feher T, Bodrogi L, Ribai Z
I. Chirurgische Klinik, Medizinische Semmelweis-Universitat, Ulloi ut 78, H-1082 Budapest, Hungary
Chirurg; 53(1):34-36 1982

Steroid hormone concentrations in plasma, in tissue from breast tumors, and in healthy breast tissue (muscle and fat) surrounding such tumors were determined by radioimmunoassays. The tissues samples were obtained from 9 patients (av age 37 yr) with benign breast tumors and 11 patients (av age 51 yr) with malignant breast tumors. The hormone concentrations in plasma were nearly identical in the two patient groups and were lower than the tissue levels. The hormone concentrations in all breast tissues of patients with benign tumors were routinely higher than the levels in breast tissues of patients with malignant tumors. (14 Refs) (In GER)

39. ABNORMAL PLASMA HORMONE LEVELS IN WOMEN WITH BREAST CANCER.

Zumoff B, Korenman SG, R
Clinical Res. Center, Montefiore Hosp. and Medical Center, Inst. for Steroid Res., Bronx, NY, 10467
Banbury Rep; 8:143-168 1981

The 24-hr mean plasma concentrations of 14 hormones or hormone metabolites were measured in breast cancer patients, patients with cancer other than breast cancer, and women with noncancerous illnesses. Normal values of triiodothyronine and elevated levels of thyroxine were found in breast cancer patients. Adrenal androgens were decreased in women with premenopausal breast cancer. Plasma levels of luteinizing hormone were normal in most patients, and subnormal in some; 24-hr profiles were abnormal in all of seven luteal phase cancer patients studied. The significance of these results is discussed. (75 Refs)

40. REPRODUCTIVE ENDOCRINOLOGY AND BREAST CANCER IN WOMEN.

Korenman SG, Lippman, Zumoff, Pike MC, Segaloff
Dept. Medicine, Univ. of California Los Angeles-San Fernando Valley Program, VA Medical Center, Sepulveda, CA, 91343
Banbury Rep; 8:71-85 1981

Normal and abnormal reproductive functions were studied focusing on the regulation of the mammary gland by the principal reproductive hormones. Interactions between estrogens, progesterone, prolactin, and conditions of estrogen excess or unopposed estrogens are presented. Because of lack of moment-by-moment assessment of the endocrine status of the breast, complex endocrine interrelations characterizing normal and abnormal reproductive cycles affecting the breast were considered only theoretically. (61 Refs)

41. HORMONAL REGULATION OF HUMAN BREAST CANCER CELLS IN VITRO.

Lippman M, Meites J, Welsch CW, Rosen JM, Segaloff A, Korenman SG, Nandi S, Sirbasku DA
Medical Breast Cancer Section, Medicine Branch, NCI, Bethesda, MD, 20205
Banbury Rep; 8:171-184 1981

Cultured breast cancer cell lines (most of which were derived from neoplastic effusions, often after treatment) differ from the original tumors in several important ways. Experiments with these cell lines must be designed and their results interpreted with great caution. Firm conclusions as to the absence of a given hormone response are particularly difficult to interpret. Positive results are much less ambiguous, but these can also give rise to misinterpretations. Nevertheless, the cell-culture approach provides several advantages in the investigation of hormonal interactions with human breast cancer. In particular, drug- and hormone-resistant variants of wild-type parental cell lines can be used to study the mechanisms of hormone dependence. Hormones now known to affect the growth or differentiated functions of human breast cancer cells (especially the MCF-7 cell line) include estrogens, glucocorticoids, androgens, thyroid hormones (the ZR-75-1 cell line is absolutely dependent on physiologic levels of triiodothyronine in the medium, and MCF-7 cells are also thyroid hormone dependent), and insulin. Vitamin A derivatives are required for normal epithelial differentiated and inhibit several types of chemical carcinogenesis in rats. Several human breast cancer cell lines contain separable binding activities for retinol and retinoic acid, but clinical trials of 13-cis-retinoic acid in breast cancer patients have not been encouraging. The roles of epidermal growth factor, vitamin D, progesterone, and prolactin in breast cancer growth are not yet clear. (46 Refs)

42. ESTROGENS AND PROGESTERONE IN HUMAN BREAST CANCER.

Cole P
Epidemiology Program, Univ. Alabama in Birmingham, Comprehensive Cancer Center, Birmingham, AL, 35294
Banbury Rep; 8:109-113 1981

The role of endogenous estrogens in induction of human breast cancer is discussed. The following questions were addressed: Is the total amount of estrogens and their balance important? Do other hormones modify the carcinogenic effects of estrogens? Is an external or environmental factor involved? Are the carcinogenic effects of estrogens maximal during a segment or phase of the menstrual cycle of woman's life? (14 Refs)

43. INFLUENCE OF PREGNANCY AND LACTATION ON EXPERIMENTAL MAMMARY CARCINOGENESIS.

Moon RC, Shellabarger CJ, Henderson BE, Pike MC, Dao TL, Meites J, Sinha YN
Life Sciences Div., IIT Res. Inst., Chicago, IL, 60616
Banbury Rep; 8:353-364 1981

The influence of pregnancy and lactation on experimental mammary carcinogenesis (MC) was studied in Sprague-Dawley female rats; 7,12-dimethylbenz(a)anthracene (DMBA)-induced MC in the rat is influenced by parity. The effect of age at which the first litter is borne on DMBA-induced MC, when

MC is initiated at a subsequent period in the life of the animal, was examined. The age at which pregnancy ensues did not appear critical in the rat. Tumor hormone responsiveness in primiparous rats appears related to the age at which pregnancy occurs; pregnancy may alter the sensitivity of mammary cells to stimulatory hormones. (19 Refs)

44. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.

Shellabarger CJ

Medical Dept., Brookhaven National Lab., Upton, NY, 11973

Banbury Rep; 8:339-351 1981

Advantages of the radiation-induced (RI) rat mammary tumor system as a mode for studying RI breast cancer in humans and the rat mammary fibroadenoma response to irradiation are discussed. Evidence for chemically induced carcinogenesis and RI carcinogenesis is compared. Estrogen synergism in mammary carcinogenesis is reviewed; women whose cancer is 'initiated' women may develop breast cancer if the disease is 'promoted,' even if the promotion occurs years after initiation. (57 Refs)

45. THE ROLE OF OVARIAN STEROID HORMONES IN MAMMARY CARCINOGENESIS.

Dao TL, Henderson BE, Welsch CW, Moon, Cole, Segaloff, Sirbascu, Zumoff BJ

Dept. Breast Surgery and Breast Cancer Res. Unit, Roswell Park Memorial Inst., Buffalo, NY, 14263

Banbury Rep; 8:281-298 1981

The role of ovarian steroid hormones on the pathogenesis of mammary cancer in both in vivo and in vitro is described. Induction of mammary cancer by ovarian hormones were studied, and the following experiments were performed: castration related to induction of mammary carcinogenesis in rats (female and male), and induction of mammary tumors by local application of the carcinogen. Studies on relationship between prolactin and estrogen in mammary tumor growth and in vitro studies of mammary carcinogenesis are presented. (19 Refs)

46. GROWTH INHIBITORY EFFECTS OF THYROID HORMONES ON ANDROGEN-DEPENDENT MAMMARY TUMOR CELLS.

Natoli C, Sica G, Natoli V, Scambia G, Iacobelli S

Laboratorio Endocrinologia Molecolare, Universita Cattolica del Sacro Cuore, Via della Pineta Sacchetti 644, 00168 Roma, Italy

J Steroid Biochem; 15:409-413 1981

Proliferative effects of thyroid hormones and their possible reaction with androgens were studied in Shionogi 115 mouse mammary carcinoma. Cells derived from this tumor are available in culture as androgen responsive (A cells) variant, whose growth is stimulated by physiological concentrations o f androgens, and as the autonomuos variant (-A cells). Presence of triiodothyronine receptors in both A and -A cells was also investigated. Correspondence between binding capacity of the nuclear receptor and biological activity of various thyroid hormone analogues suggests that the proliferative effect is mediated via a receptor mechanism. (23 Refs)

47. EFFECT OF THYROID HORMONES ON ANDROGEN RESPONSIVENESS IN A MAMMARY TUMOR CELL LINE.

Sica G, Natoli C, Marchetti P, Iacobelli S

Istituto di Istologia ed Embriologia Generale, Universita Cattolica del Sacro Cuore, Largo Gemelli 8, 00168 Roma, Italy

J Steroid Biochem; 15:415-419 1981

Effects of thyroid hormones (TH) on androgen responsiveness (AR) were studied in Shionogi mouse mammary carcinoma cells (S115) and the variability of hormone response and duration of endocrine-induced remissions in human cancer regressions was investigated. Triiodothyronine (T3) at physiological concentrations slows down the loss of AR in S115 cells, cultured in the absence of testosterone. This is not mediated by the androgen receptor, since its level remains constant. T3 effect is more evident in the presence of AG1 x 10 anion-exchange resin which depletes serum of TH. (15 Refs)

48. ESTROGEN-INDUCED SYNTHESIS AND SECRETION OF PROTEINS IN THE HUMAN BREAST CANCER CELL LINE MCF-7.

Mairesse N, Devleeschouwer N, Leclercq G, Galand P

Biology Unit, Inst. Interdisciplinary Res., Sch. Medicine, Free Univ. Brussels, 2 rue Evers, 1000-Brussels, Belgium

J Steroid Biochem; 15:375-381 1981

Estrogen-induced synthesis and secretion of proteins (IP) were studied in the human breast cancer cell line MCF-7, the association of creatine kinase activity with IP fraction was tested, and the potential relationship of IP with cytosolic and secreted proteins was investigated and results compared with other studies. IP was resolved into two major proteins of 52,000 and 46,000 mol wt and two minor ones of 54,000 and 60,000 mol wt. Estradiol stimulated within 2 hr the synthesis of the four proteins in the responsive MCF-7 cell line, but not in the Evsa-T cells which lack the estrogen receptors. (23 Refs)

49. PLASMA PROLACTIN ANALYSIS AS A POTENTIAL PREDICTOR OF MURINE MAMMARY TUMORIGENESIS.

Sinha YN, Siiteri, Dao TL, Meites J, Rosen JM, Korenman, Shiu, Sirbasku DA

Lutcher Brown Center for Diabetes and Endocrinology, Scripps Clinic and Res. Foundation, La Jolla, CA, 92037

Banbury Rep; 8:377-394 1981

The correlation between plasma prolactin (PP) and breast cancer (BC) in humans, rats, and mice and possible reasons for the lack of correlation between PP and BC (metabolic clearance rate of prolactin (PR), conversion of PR into nonimmunodetectable forms, size heterogeneity of circulating PR, and immunologically unreactive form of PR in the pituitary) are discussed. A clinical correlation between PP and incidence of BC has not been found, possibly due to a lack of methods for quantification of all different molecular forms of PR present in the blood. (53 Refs)

50. PROLACTIN AND GROWTH HORMONE IN THE DEVELOPMENT, PROGRESSION, AND GROWTH OF MURINE MAMMARY TUMORS.

Welsch CW
Dept. Anatomy, Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:299-315 1981

The role of prolactin and growth hormone in the development and growth of spontaneous rodent mammary tumors, were examined. Growth of transplantable rodent mammary tumors, and development and growth of carcinogen-induced rat mammary tumors were also examined. Prolactin is important in initiating and promoting phases of murine mammary tumorigenesis, while the role of growth hormone appears to be less important. The role of growth hormone in the oncogenesis remains to be determined. (72 Refs)

51. INTERACTION OF PROLACTIN, ESTROGEN AND PROGESTERONE IN A HUMAN MAMMARY CARCINOMA CELL LINE, CAMA-1. I. CELL GROWTH AND THYMIDINE UPTAKE.

Leung BS, Potter AH, Qureshi S
Dept. Obstetrics and Gynecology, Univ. Minnesota, Box 395 Mayo Memorial Building, 420 Delaware St. S.E., Minneapolis, MN, 55455
J Steroid Biochem; 15:421-427 1981

The growth and thymidine (TDR) uptake of a human mammary carcinoma cell line (CAMA-1) in long term monolayer culture were investigated. The cells were maintained in the log phase for 7 days in Eagles' minimum essential medium with Earle's salt, supplemented with 15 or 25% fetal bovine serum (FBS) without further feeding. The effects of FBS, dextran-charcoal treated FBS (DCFBS), and serum substitute (SS) were investigated. CAMA-1 cells grew poorly in SS as compared to 25% FBS. With addition of either 1% FBS or DCFBS cell proliferation in SS substantially improved. Ten percent SS plus 10% DCFBS yielded fewer cells on day 7 than conditions with SS plus 1% serum. Apparently, FBS must also contain certain inhibitors of cell growth. When cells were grown in the absence of added estradiol (ED) in DCFBS, cell growth was substantially reduced. Effect of ED is dose-dependent, 0.1 milliM inhibited and 10 nanoM stimulated cell growth. Estrogen (ES) not only stimulated cell growth, it also stimulated the uptake of TDR into cells. Prolactin (PR) by itself, or even in the presence of ES, had no effect upon cell proliferation. The effect of combined treatment with ES and PR on TDR uptake into cells was examined in 10% DCFBS and 10% SS plus 1% DCFBS. ED in absence of PR affected an approx 1.5-fold increase of TDR uptake; with SS, no ED-induced TDR uptake was exhibited. A dichotomous effect of progesterone (PG) upon TDR was observed, low levels of PG had only slight stimulatory effect and had additional stimulation upon ES-induced TDR uptake. PG at 10 uM uniformly inhibit ed TDR uptake either in the presence or absence of ED. Results indicate that the CAMA-1 cell line is a good alternative model for the investigation of hormonal interaction. (23 Refs)

52. PROLACTIN - AN IMPORTANT HORMONE IN BREAST NEOPLASIA?

Henderson BE, Pike MC, Moon RC, Segaloff A, Bulbrook RD, Meites J, Siiteri PK, Shellbarger CJ, Cole P
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep; 8:115-130 1981

The role of prolactin in the development and growth of breast tumors is discussed. After the first full-term pregnancy, a woman's plasma prolactin level may be permanently lowered, perhaps providing protection against the development of breast cancer. Breast cancer patients and their high-risk family members generally have elevated prolactin levels. Prolactin level has not been correlated with wt or any dietary nutrients. Prolactin may enhance the mitogenic effect of estrogen. (30 Refs)

53. THE ACTIONS OF INSULIN AS A HORMONAL FACTOR IN BREAST CANCER.

Hilf R, Siiteri PK, Shellabarger, Korenman SG, Rosen, Nandi
Dept. Biochemistry and Univ. Rochester Cancer Center, Univ. Rochester, Rochester, NY, 14642
Banbury Rep; 8:317-337 1981

Evidence implicating insulin as one of the hormones involved in the growth of breast cancer in animals (insulin-dependent and insulin-responsive tumors) is presented. Some of insuline actions related to neoplastic growth are described (insulin receptors and their regulation, insulin and glucose transport, insulin and amino acid transport, and insulin as a regulator of estrogen receptors). Clinical data and the role of insulin in human breast cancer are reviewed. Direct effects of insulin are stimulation and inhibition of tumor growth. Indirect effects are regulation of estrogen receptors and antagonism of insulin effects by estrogen. (73 Refs)

54. ROLE OF HORMONES IN MAMMOGENESIS AND CARCINOGENESIS.

Nandi S, Yang J, Richards J, Guzman R, Shellabarger CJ, Rosen JM, Sirbasku DA, Siiteri PK, Korenman SG
Dept. Zoology and Cancer Res. Lab., Univ. California, Berkeley, CA, 94720
Banbury Rep; 8:445-456 1981

Development of a collagen system for growing mammary cells in vitro is described. Results for general aspects of growth of mammary cells inside collagen gel matrix (CGM), growth of normal mouse mammary epithelial cells (MEC) inside CGM (effects of hormones and growth factors), and for growth of normal human MEC inside CGM (effects of hormones and tissue extracts) are presented. Explanation for the observation that mammogenic hormones are growth-promoting in vivo appears to be in the fact that hormone-induced growth of a tissue or organ in vivo is a complicated phenomenon encompassing a number of biological events at the tissue level, including cell division; hormones might be the ultimate regulators of tissue growth, although they are not directly mitogenic. (27 Refs)

55. MECHANISMS OF ESTROGEN AND ANTIESTROGEN ACTION IN MAMMARY CANCER.

Katzenellenbogen BS, Rorke EA, Eckert RL
Dept. Physiology and Biophysics, Univ. Illinois, Urbana, IL, 61801
J Steroid Biochem; 15:219-229 1981

Estrogen antagonist and estrogen agonist actions of antiestrogens (AE) in ovarian-dependent and autonomous rat mammary tumors (RMT) and in human MCF-7 breast cancer cells were studied. RMT were 7,12-dimethylbenz(a)anthracene (DMBA)-induced in virgin female Sprague-Dawley rats. R3230AC RMT were induced in 40-day-old female Fischer 344 rats. After U23,469 treatment, approx 90% of receptors are found in the nucleus, and the progesterone receptor level is similar to that of the controls and is considerably higher than in RMT regressing due to ovariectomy. AE also influence the level of prolactin binding in DMBA-induced RMT. Administration of U23,469 and two related AE, U11,100A and CI628, beginning at the time of R3230AC tumor transplantation resulted in 2-4 fold depression of tumor growth rate, and the degree of reduction is related to the dose of AE. R3230AC tumor growth is also depressed by estradiol-17 beta while growth is at or slightly above the control rate in ovariectomized hosts. AE treatment increased peroxidase activity (PA) 3-fold, and when AE was administered along with estradiol, mammary tumor PA was only stimulated to the level seen with AE alone. Ovariectomy had no effect on the level of PA in tumors. In vivo studies in the rat utilizing tritium labeled AE revealed that AE are converted to metabolites with increased binding affinity (BA). U23,469 metabolites BA is 50x greater than that of U23,469, while CI628 metabolite binds approx 20x better than the parent compound. Results suggest the existence of differences in chromatin interaction that may underlie the antagonist character of AE. (51 Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

56. PREDICTIVE VALUE OF TUBE LEUKOCYTE ADHERENCE INHIBITION (LAI) ASSAY FOR BREAST, COLORECTAL, STOMACH AND PANCREATIC CANCER.

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Cancer; 49(6):1185-1193 1982

The tube LAI assay measures accurately antitumor immunity in patients with early cancer but fails to detect up to 75% of patients with advanced cancer due to excess circulating organ-specific neoantigen (OSN). Substances such as prostaglandin E2 (PGE2) or aminophylline which increase intracellular nucleotides in leukocytes of patients with advanced cancer reversed this nonreactivity and greatly increased the sensitivity of the assay without any loss of specificity. Antitumor immunity can now be dete cted in advanced cancer, and a combination of the two assays gives prognostic potential to the assay: a positive test with PGE2 and negative test without indicates the patient has a large tumor burden. The specificity of the assay for each cancer was high and in most instances was greater than or equal to 95%. The PGE2 stimulated assay retained the high specificity. The sensitivity of the regular tube assay was often low, 33-56% because of the many advanced cancer patients tested, whereas the PGE2 stimulated assay showed almost a two-fold increase in sensitivity, 67-93%. The diagnostic value of the assay was estimated by calculating the predictive value for different prevalences of cancer. It was found that at low prevalences of cancer as found in the general population, the assay had a low diagnostic value since few patients with a positive test would have the cancer tested for. With prevalences of cancer of 5% or greater as might be found in a tertiary care clinical setting, the assay would seem to have diagnostic value since one half or more patients with a positive test would have the cancer tested for. Most false positives, but not all, are found in patients who have lesions that are often considered to increase their risk for cancer: severe dysplasia of breast, colon adenomas, chronic atrophic gastritis ad chronic pancreatitis, suggesting that the assay predicts oncogenesis. (Author abstract) (35 Refs)

57. IDENTIFICATION OF LYMPHOCYTE SUBPOPULATIONS IN HUMAN BREAST CANCER TISSUE AND ITS SIGNIFICANCE: AN IMMUNOPEROXIDASE STUDY WITH ANTI-HUMAN T- AND B-CELL SERA.

Shimokawara I, Imamura M, Yamanaka N, Ishii Y, Kikuchi K
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Cancer; 49(7):1456-1464 1982

Subpopulations of the infiltrating lymphocytes in breast cancer tissue from 31 patients were identified by indirect immunoperoxidase technique with antihuman T- and B-cell sera. In all noncancerous lesions examined (7 cases), B-cells were predominant and T-cells were scarcely found. In contrast, T-cells were predominant in breast cancer tissues (17 in 21 cases). T-cells tended to contact closely with cancer cells or cancer cell nests and accumulated around and in the walls of venules draining the cancer, while B-cells tended to cluster focally apart from cancer cell nests. T-cell infiltration was scanty in scirrhus carcinoma, whereas it was ample in infiltrating papillotubular carcinoma which had a better prognosis. There was a significant reverse correlation between the intensity of the T-cell infiltration and the clinical stages. The intensity of the T cell infiltration was significantly high in patients without lymph node metastasis. These facts suggest the possibility that the infiltrating T-cells in cancer tissue represent host resistance against cancer and that the intensity of the T cell infiltration correlates with the clinical prognosis of the breast cancer patients. (Author abstract) (31 Refs)

58. EVALUATION OF ANTIBODY-DEPENDENT CELL CYTOTOXICITY (ADCC) AND SPONTANEOUS LYMPHOCYTE-MEDIATED CYTOTOXICITY (SLMC) IN PATIENTS SUFFERING FROM MALIGNANT DISEASE.

Degliantoni G, Mangoni L, Manna A, Funcini M
Cattedra di Ematologia - Clinica Medica Generale e Terapia Medica, Universita degli Studi di Parma, Parma, Italy
G Clin Med; 62(9):609-623 1981

The immune system and the evolution of malignant neoplasia were studied in 36 patients with cancer. Lymphocytes B, T, and EA rosette formation were determined in normal controls (NC: 20-70 yr old patients) with different diseases (DD), with localized cancer (LC: pulmonary, mammary, digestive tract, melanomas etc), with metastasizing cancer (MC: mammary cancer with bone and brain metastases, colon cancer with hepatic metastases and bladder cancer with bone and lymph node metastases), patients receiving polychemotherapy (PCT) with 5-fluorouracil and dacarbazine, patients receiving cyclophosphamide (CYP), and patients receiving radiotherapy (RT). Antibody-dependent cell cytotoxicity (ADCC) and spontaneous lymphocyte-mediated cytotoxicity (SLMC) were present in all NC with values slightly lower in older persons and women. The values for lymphocytes B, T, and EA rosette for NC were on the av 10%, 55%, and 8%, respectively, for DD the values were 8%, 53%, and 7% respectively, for not treated LC the values were 7%, 47%, and 7%, respectively, for not treated MC were 8%, 41%, and 6% respectively, for PCT were 7%, 38%, and 6%, respectively, for treated with CYP the values were 4%, 22%, and 3%,respectively, and for treated with RT the values 2%, 7%, and 2%, respectively. Natural Killer cell activity was significantly decreased in MC patients. Differences of lytic response in vitro were not related to T/B lymphocyte ratio in 90% of the cases. (5 Refs) (In ITA)

59. PATIENTS' IMMUNE RESPONSE TO BREAST AND LUNG SPECIFICITY.

Springer GF, Murthy SM, Desai PR, Fry WA, Tegtmeyer H, Scanlon EF
Immunochemistry Res., Evanston Hosp., 2650 Ridge Ave., Evanston, IL, 60201
Klin Wochenschr; 60(3):121-131 1982

We report here sensitive and specific measurement of immune responses of patients with certain kinds of carcinoma toward the physically and chemically well defined T antigen isolated from healthy human erythrocytes. Over 90% of adenocarcinoma tissues tested possess T-specific immunoreactive structures as determined with human antisera, in contrast to healthy tissues and benign lesions. Adenocarcinoma patients recognize the carcinoma-associated T antigen as foreign. Delayed-type skin hypersensitivity reaction to T antigen (DTHR-T) was tested. In vitro leukocyte migration inhibition and scoring of anti-T hemagglutinin titer using the T-anti-T system diagnosed many adenocarcinomata correctly, but these tests were generally less sensitive and specific than the DTHR-T. This system may also be of screening and monitoring value. Surgical removal of primary carcinoma led to a rebound of anti-T in breast carcinoma patients and its renewed decrease in some, prior to clinical recurrence of cancer. Also, the DTHR-T turned from positive to negative in some Stages I and II breast and T1-2 N0-1 M0 lung adenocarcinoma patients who had no demonstrable relapse during the ensuing observation period. (75 Refs)

60. IMMUNOLOGIC STATE OF PATIENTS WITH OPERABLE MAMMARY CANCER.

Hrsak KM, Rudolf M, Kubovic M, Martinac P, Bulic N, Katelan M
Zavod za klinicku onkologiju i radioterapiju, Klinicki bolnicki centar, Rebro, Zagreb, Yugoslavia
Libri Oncol; 10(2/3):323-326 1981

Immunologic state was evaluated in 44 healthy controls (HC) and in 49 patients with operable mammary cancer (MC) in different stages of the disease with the aid of mitogens reactivity [phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM)], T and B lymphocytes, and the most active T lymphocytes (E, M, and A rosettes) in peripheral blood. Patients were tested before receiving any therapy. Reactivity to mitogens was lower in MC compared with HC patients. Most pronounced reactivity was seen when tested with PHA. Difference in reactivity between Stage I and the other two could be observed. Total number of T and B lymphocytes was reduced, but that reduction was less significant than the reactivity to mitogens. Most active T lymphocytes were higher in Stage II patients with MC than in HC. (8 Refs) (In SCR)

61. PROSPECTIVE EVALUATION OF THE LEUKOCYTE ADHERENCE INHIBITION (LAI) TEST IN BREAST CANCER USING A PANEL OF EXTRACTS FROM KNOWN AND UNKNOWN PRIMARY TUMORS.

Fritze D, Kaufmann M
Medizinische Universitatsklinik, D-69 Heidelberg, W. Germany
Int J Cancer; 29(3):261-264 1982

The antigen-induced leukocyte adherence inhibition (LAI) test is an assay of cellular immune reactivity which was expected to offer a promising adjunct to currently available diagnostic and monitoring procedures in cancer patients. We have applied this assay to 83 inpatients clinically suspected of having breast cancer, 50 outpatients before mammography, and 37 healthy women. In order to account for the known heterogenicity of breast cancer, we performed LAI assays with extracts from 15 primary tumors of known and 14 primary tumors of initially unknown histology. Thus, the problem of tumor specificity in the LAI assay was tackled in a double-blind fashion. The results obtained clearly show that breast-tissue-specific rather than tumor-specific responses were detected by LAI testing. The LAI assay failed to discriminate between high-risk patients with and without cancer and between extracts from breast tumors with and without carcinoma. The results are discussed with regard to the many claims for the detection of specific tumor immunity in the literature. (Author abstract) (25 Refs)

62. INVESTIGATION OF CIRCULATING IMMUNE COMPLEXES IN PATIENTS WITH BREAST CANCER.

Horvath M, Fekete B, Rahoty P
Natl. Inst. Oncology, P.O. Box 21, 1525 Budapest, Hungary
Oncology; 39(1):20-22 1982

Circulating immune-complex (IC) levels of patients with breast cancer were measured before and after surgery using a complement-consumption technique. Sixteen of 26 patients showed raised pre-operative IC values. In 15 out of 16 patients the pathological IC levels decreased within 2-10 days following surgery. Suggestions about the applicability of this test not only for prognosis, but also for monitoring the course of breast cancer need to be confirmed by further investigations. (Author abstract) (15 Refs)

63. 'HIDDEN' CYTOTOXIC ANTIBODIES THAT REACT WITH ALLOGENEIC CULTURED FETAL AND TUMOR CELLS CONTAINED IN SOLUBLE IMMUNE COMPLEXES FROM NORMAL HUMAN SERA.

Morgan AC, Rossen RD, McCormick KJ, Stehlin JS, Giovanella BC
(c/o Rossen) Immunology Res. Lab., Veterans Admin. Medical Center, Building 211, Room 203, 2002 Holcombe Blvd., Houston, TX, 77211
Cancer Res; 42(3):881-887 1982

Hidden complement-dependent cytotoxins were demonstrated in normal donor sera after removing anti-immunoglobulins that normally block the ability of these immunoglobulin Gs to react with surface antigens on tumor cells. The blocking antibodies had certain properties of anti-idiotypes. Immunoglobulin G from Cohn Fraction II, after removing these anti-immunoglobulins, was cytotoxic for cultured fetal cells and for malignant melanoma, breast, lung, colon, and other tumor cells maintained either in tissue culture or by serial passage in nude mice. The cytotoxins were not adsorbed by extracts from normal lymphoid, liver, skin, or red blood cells. These results suggest that a heterogeneous group of natural antibodies reactive with antigens expressed on a variety of neoplastic and fetal cells circulate in normal donor sera as part of a soluble immune complex, together with a blocking anti-immunoglobulin. (Author abstract) (39 Refs)

64. C1Q SOLID-PHASE ENZYMATIC MICROASSAY FOR DETECTION OF CIRCULATING IMMUNE COMPLEXES: ITS APPLICATION IN HUMAN BREAST CANCER.

Manzo C, Longo C, Bianchin A
Istituto Tumori Fondazione Pascale, Via M. Semmola, Cappella Cangiani, 80131 Napoli, Italy
Tumori; 68(1):47-52 1982

Circulating immune complexes (CIC) were detected and quantitated in human breast cancer to monitor the efficiency of mastectomy. For this aim a microimmunoenzymatic test was set up, applying a solid-phase C1q. Features of this assay can be summarized as follows: ability to estimate as low as 10 ng of aggregated human IgG (deltaIgG), good reproducibility and simplicity of execution, and small serum sample required. A group of women with breast cancer at different stages (TNM classification) was tested for CIC, and 31.75% were positive. Almost all patients submitted to surgery showed a reduction of this parameter thereafter. A parallel study was carried out in another group of women with benign breast disease, and a significant incidence of CIC was found. (Author abstract) (19 Refs)

65. SELECTIVE DECREASE OF IGE BLOOD LEVEL IN PATIENTS WITH CERTAIN MALIGNANT TUMORS.

Grinevich IuA
Res. Roentgenoradiological and Oncological Inst., Kiev, USSR
Vrach Delo; (12):90-93 1981

The role of IgE in the antitumor immunity was studied in 102 patients with precancerous breast diseases and in 372 patients with breast cancer (168 had Stage I-II, 145 had Stage III, and 59 had Stage IV). The blood levels of IgA, IgM, and IgG were assayed by radial immunodiffusion. The blood level of IgE was determined by radioimmunoassay. The IgM levels in the patients in Stages I-II, III, and IV were 1.1, 1.08, and 1.01 mg/ml, respectively, compared with 1.05 mg/ml in healthy controls and 1.2 mg/ml in the patients with precancerous breast diseases. The blood levels of IgG in patients in Stages I-II, III, and IV were 17.0, 16.6, and 18.7 mg/ml, respectively, compared with 15.3 mg/ml in healthy controls and 16.4 mg/ml in the patients with precancerous conditions. The corresponding levels of IgA were 3.7, 3.7 and 4.4 mg/ml, vs 3.1 and 3.5 mg/ml, respectively. All patients with breast cancer showed marked decrease of IgE level: 18.7 44.6, and 20.4 nanog/ml in Stages I-II, III, and IV, respectively, compared with 202.5 nanog/ml in healthy controls. (3 Refs) (In RUS)

66. MONOCLONAL ANTIBODIES TO THE HUMAN MAMMARY GLAND. I. DISTRIBUTION OF DETERMINANTS IN NON-NEOPLASTIC MAMMARY AND EXTRA MAMMARY TISSUES.

Foster CS, Edwards PA, Dinsdale EA, Neville AM
Ludwig Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 GPX, England
Virchows Arch [Pathol Anat]; 394(3):279-293 1982

Mouse monoclonal antibodies have been raised to the human milk fat globule membrane. The distribution of the antigens detected by four of the antibodies has been examined in formalin-fixed, paraffin-embedded human tissues by light microscopic immunocytochemistry. The four antibodies stain lactating breast and normal resting breast. Two exclusively stain the luminal membranes of breast epithelial cells. A third antibody stains in addition the lateral membranes of duct epithelial cells. The fourth antibody stains both epithelial and myoepithelial cells. None of the antibodies is breast specific, nor do they stain every epithelial cell within the breast. Instead, each antibody reveals a complex and heterogeneous distribution of staining throughout the normal tissues. Within the breast, the staining by a given antibody is usually segmental and conforms to secretory units and their associated ducts. Similarly heterogeneous patterns of staining are also observed in the extramammary normal tissues. Despite the apparent morphological identity between breast epithelial cells when examined by conventional light microscopy, the hitherto unrecognized 'functional' heterogeneity, which as been revealed by the monoclonal antibodies could have importance in understanding the biology of the normal breast and the pathology of breast cancer. (Author abstract) (18 Refs)

67. MONOCLONAL ANTIBODIES TO THE HUMAN MAMMARY GLAND. II. DISTRIBUTION OF DETERMINANTS IN BREAST CARCINOMAS.

Foster CS, Dinsdale EA, Edwards PA, Neville AM
Ludwig Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England
Virchows Arch [Pathol Anat]; 394(3):295-305 1982

A range of primary and metastatic human breast carcinomas has been examined with respect to the staining by four monoclonal antibodies which were raised to the human milk fat globule membrane. Within the normal breast the luminal epithelial cells expressing the antigens detected by the monoclonal antibodies were heterogeneous in their distribution. The heterogeneity was not only confined to single cells, but also to regions within the breast. The breast carcinomas also expressed the antigens in a variable manner. Morphological differentiation and functional differentiation, defined by the monoclonal antibodies, were not invariably coincident. Lymph node metastases gave similar results to the primary carcinomas. The monoclonal antibodies have revealed a heterogeneity, with respect to surface antigenic expression, within the normal and neoplastic breast epithelium. This cellular heterogeneity of breast carcinomas, may have significant prognostic and therapeutic implications in the management of primary breast cancer. (Author abstract) (17 Refs)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

68. MOUSE MAMMARY TUMOUR VIRUS AND POLYOMA VIRUS INFORMATION IN MAMMARY TUMOURS OF ATHYMIC MICE INOCULATED WITH POLYOMA VIRUS.

Arya SK, Galarraga JJ
Lab. Tumor Cell Biology, NCI, NIH, Bethesda, MD, 20205
J Gen Virol; 58(part1):107-114 1982

Polyoma virus inoculation of athymic mice results in the development of mammary tumors with a much higher incidence than the development of salivary gland tumors, the latter being the most common for immunocompetent normal mice. The possibility existed that polyoma virus might act as a co-carcinogen in activating the expression of mouse mammary tumor virus (MMTV). Molecular hybridization studies, however, showed that the mammary tumor development was accompanied by neither the amplification of MMTV genomic sequences nor by their more extensive transcription. In contrast, tumor tissue contained about 60 to 100 copies of polyoma virus genome equivalents per cell and some of these sequences were apparently transcribed into RNA. While these results do not rule out the transient involvement of MMTV expression in mammary tumor development, it appeared that the mammary gland cells were directly transformed by polyoma virus. Apparently, polyoma virus displayed a tropism in athymic mice that was different from that in normal mice. (Author abstract) (30 Refs)

69. ORGANIZATION OF PROVIRAL DNA AND PROTEIN COMPOSITION OF HORMONALLY STIMULATED C57BL/10 STRAIN-ASSOCIATED MOUSE MAMMARY TUMOR VIRUS.

Svec J, Matoska J, Keszeghova V, Hlavayova E
Cancer Res. Inst., Slovak Acad. Sciences, 812 32 Bratislava, Czechoslovakia
Neoplasma; 28(6):647-659 1981

Two continuous lines, BL-MaTU/A1 and BL-MaTU/S6, were established from C57Bl/10 mammary adenocarcinomas induced by DMBA-prolactin-estradiol treatment. Under in vivo stimulation with dexamethasone, insulin, prolactin, and prostaglandin A1, the cells produce detectable amounts of B-type particles with biochemical properties similar to the GR-MuMTV. Analysis of restriction endonuclease-generated fragments of cellular DNA revealed identical patterns in the integration sites and internal recognition sites of MuMTV proviral equivalents in the tumor cells and normal organs of C57Bl/10 strain mice. The restriction DNA fragments of C57Bl/10-associated MuMTV proviral DNA are closely related to those of the Balb/c-associated MuMTV. These results indicate the endogenous origin of MuMTV produced in the hormonally stimulated cultures of DMBA-prolactin-estradiol-induced C57Bl/10 mammary tumors. (Author abstract) (35 Refs)

70. RESTRICTION ENDONUCLEASE MAPPING OF THE PROVIRAL DNA OF THE EXOGENOUS RIII MURINE MAMMARY TUMOR VIRUS.

Etkind PR, Szabo P, Sarkar NH
Lab. Molecular Virology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Virol; 41(3):855-867 1982

Cellular DNA containing integrated murine mammary tumor virus (MuMTV) was isolated from FeI/C6 feline kidney cells and CCL64 mink lung cells infected with milkborne RIII MuMTV. By using restriction enzyme HpaI, intact RIII MuMTV provirus (length, 8.7 kilobases [kb]) was excised from the cellular DNA. Subsequent restriction endonuclease analysis of this HpaI fragment with KpnI, HindIII, EcoRI, BamHI, BglII, PstI, SstI, SalI, and XhoI enabled us to construct a map of the RIII virus genome. A comparison of this map with the maps of the GR and C3H MuMTV's revealed that there are greater sequence differences between the RIII virus and the GR and C3H MuMTV proviruses than there are between the GR and C3H proviruses. The following are features of the restriction map unique to the RIII provirus: the presence of three BamHI and two EcoRI cleavage sites, a HpaI cleavage site in the terminal 3'-5' repeat unit of the provirus, and the absence of an XhoI cleavage site. Another distinguishing feature of the RIII provirus is that the sizes of some of the restriction fragments produced by cleavage of the RIII provirus with PstI are different from the sizes of the fragments obtained by PstI cleavage of the GR and C3H proviruses. Like the GR proviral DNA, the RIII proviral DNA has three SstI (SacI) cleavage sites, whereas the C3H provirus has only two SstI sites. HpaI digestion of MuMTV-infected mink lung cell DNA revealed only one class of provirus (an 8.7-kb fragment); however, we observed minor classes of RIII proviral DNA in addition to the major class of provirus DNA in infected cat kidney cells. PstI digestion of the HpaI 8.7-kb fragments from both feline and mink cells generated a 3.7-kb DNA fragment identical in size to a PstI-generated fragment that has been found in GR and C3H milkborne virus-infected cells. Although a fragment similar in size to the milkborne 3.7-kb PstI fragment has been found an endogenous component fragment in the RIII mouse strain. Therefore, the 3.7-kb fragment may be useful as a marker for the milkborne RIII MuMTV provirus in RIII mice. (Author abstract) (50 Refs)

71. METHYLATION AND AMPLIFICATION OF MOUSE MAMMARY TUMOR VIRUS DNA IN NORMAL, PREMALIGNANT, AND MALIGNANT CELLS OF GR/A MICE.

Fanning TG, Vassos AB, Cardiff RD
Dept. Pathology, Sch. Medicine, Univ. California, Davis, CA, 95616
J Virol; 41(3):1007-1013 1982

The methylation and amplification of mouse mammary tumor virus (MuMTV) proviral DNA was investigated in normal, premalignant, and malignant tissues of GR/A mice. The proviral methylation pattern was examined with the restriction enzyme HhaI, which fails to cleave methylated DNA. MuMTV proviral DNA from liver, kidney, and heart was highly methylted. Proviral DNA was somewhat undermethylated in mammary gland cells from virgin and lactating mice and extensively undermethylated in cells from premalignant outgrowths, pregnancy-dependent tumors, and pregnancy-independent tumors. The restriction enzyme SacI was used to detect additional proviruses in the same cells. No additional proviral copies of MuMTV were detected in liver, kidney, or heart cells or in mammary gland cells from virgin mice. Some mammary gland cells from lactating mice appeared to contain additional copies of the endogenous, highly oncogenic GR-MTV-2 provirus. Premalignant outgrowth, pregnancy-dependent tumor, and pregnancy-independent tumor cells contained an average of two to three additional copies per cell of the GR-MTV-2 provirus. Thus, neoplasia in GR/A mice was directly associated with quantized increases in MuMTV proviral DNA undermethylation and GR-MTV-2 proviral DNA amplification. Restriction enzyme analysis suggested that premalignant outgrowths and pregnancy -dependent tumors both consisted largely of heterogenous cell populations, although some evidence of clonal dominance was detected. (Author abstract) (31 Refs)

72. EFFECTS OF STEROIDS ON VIRAL INFECTION OF HUMAN BREAST CANCER CELL LINES BY ADENOVIRUS 5.

Chouvet C, Chardonnet Y, Saez S
Centre Leon Berard, 28 rue Laennec, 69372 Lyon Cedex 2, France
J Steroid Biochem; 15:269-274 1981

Effects of steroid hormones, especially estradiol (ES), on the infection of MCF7, a human epithelial cell line established from a metastatic breast adenocarcinoma, by adenovirus 5 were studied. Cytopathy induced by viral infection occurred 24 hr earlier in the presence of 10(-8) M ES. Some differences in the synthesis of viral proteins were detectable at 32 hr, and at 40 hr 78% of cells grown in the presence of hormone were positive vs 44% in the control. Potentiation of viral production is significant after 29 hr of infection and is max from 37 to 48 hr. The quantity of complete infectious particles produced in the control without hormone was very small for low virus concentrations [10 plaque forming units (PFU)/ cell] and increased with the dose of virus used. In the presence of ES, the difference with control was max for low infectious doses. Cells infected in the presence of 10(-9) M ES did not produce more viral particles than controls, but the addition of 10(-8) M ES amplified the number of PFU produced/cell approx 10x. Hormone deletion after infection did not decrease the production of viral particles. Whether the hormone was deleted for 2 or 4 hr before infection, the increase in viral production occurred as if hormone were present. The hormonal effect is apparently steroid specific and requires the corresponding receptors. More viral DNA is synthesized in the presence of hormone and max effect occurs later in the presence of hormone. No evidence was obtained for the synthesis of a protein specific to the hormonal effect, but the kinetics of synthesis were different between the hormone treated and untreated cultures. (26 Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

73. IS A FUNCTIONAL ESTROGEN RECEPTOR ALWAYS REQUIRED FOR PROGESTERONE RECEPTOR INDUCTION IN BREAST CANCER?

Horwitz KB
Dept. Medicine and Biochemistry, Univ. Colorado, Health Science Center, Denver, CO, 80262
J Steroid Biochem; 15:209-217 1981

Presence of a functional estrogen receptor (ER) as a requirement for progesterone receptor (PR) induction in breast cancer (BC) was studied in the T47D human BC cell line. ER and PR were measured after 30 passages in modified medium. Cells had less than 0.04 picomole/mg DNA of specific, unfilled ER in the cytoplasm when measured on a sucrose gradient. ER are anomalous: 10 nanoM estradiol treatment failed to deplete and translocate cytoplasmic receptors, and nuclear receptors failed to be subsequent ly processed. ER of T47D cells also have an unusual response to the estrogen antagonist, nafoxidine, cell growth is not inhibited and minimal effects on PR were observed. PR are heat labile, sediment at 7-8S on sucrose gradients, and specifically bind progestins. After 0.1 uM progesterone treatment (PT) PR rapidly (1-2 min) move out of the cytoplasm and into the nuclei. One hr of PT depleted PR, and these were fully restored in 10-24 hr when progesterone was removed, indicating that the cells are either functionally ER-negative, or the ER are in a permanently activated state in the nucleus. Nafoxidine reverses this activated processed state. After 4 days on 20 ug/ml B-bromodeoxyuridine PR levels were reduced 70%. This effect was completely prevented by addition of excess thymidine (10x). When T47D cells were cultured in the presence of 10 milliM butyrate, PR levels fell 32% in 24 hr, and 55% in 36 hr. The inhibitory effect was completely reversible even after 72 hr, if the compound was removed from the medium. Results suggest that transcription of the PR gene in T47D cells is not constitutive, but remains at least partially regulated. (30 Refs)

74. HORMONE DEPENDENCE OF EXPERIMENTAL MAMMARY TUMORS INDUCED BY AN ESTRADIOL-PROGESTERONE COMBINATION.

Hannouche N, Samperez S, Riviere MR, Jouan P
Laboratoire de Biochimie des Hormones, Centre Regional de Recherche en Endocrinologie, Campus de Beaulieu, 35042 Rennes Cedex, France
C R Soc Biol (Paris); 175(6):744-748 1981

Levels of estradiol (ER) and progesterone (PR) receptors were determined in male rats treated with implants of a combination of 17-beta-estradiol (20 mg) and progesterone (100 mg). Mammary tumors usually appeared within 6 mo of hormone treatment, increasing to the size of a hazel-nut within 7-8 mo of treatment. Multiple tumors were present in some rats. Two types of tumors were observed: edematous tumors consisting of abnormal cells with slightly basophilic cytoplasms and clear, nucleated nuclei histologically similar to large glandular tumors; and fibrous tumors with proliferations of abnormal intragalactophorous cells and very abundant and fibrous tissue. Characteristics of experimental mammary tumors were identical to those of human breast tumors. All of the mammary tumors analyzed had ER. In the cytosol, the majority of ER sites were occupied by endogenous hormone; few if any free ER were observed. The level of ER in the nucleus was usually greater than that of the cytoplasm. Tumor heterogeneity was observed. Tumor PR were found in 6/8 tumors analyzed. In general, levels of PR were elevated and superior to those of ER. (8 Refs) (In FRE)

75. PROLACTIN, PITUITARY HORMONES, AND BREAST CANCER.

Shiu RP, Lippman M, Rosen JM, Sirbasku DA, Welsch CW
Dept. Physiology, Faculty Medicine, Univ. Manitoba, Winnipeg, Manitoba R3E OW3, Canada
Banbury Rep; 8:185-196 1981

The number of prolactin receptors (PR) in 11 human breast cancer cell lines ranged from 25,800 to 1,094; there were 1,700 in a normal cell line. The biological significance of PR and biological responses produced by PR are discussed. No growth-regulatory effect of prolactin has been demonstrated. In vivo, human breast cancer cells were responsive to estrogen and pituitary hormones. (25 Refs)

76. STRUCTURAL SIMILARITY OF MOLYBDATE-STABILIZED STEROID RECEPTORS IN HUMAN BREAST TUMORS, UTERI AND LEUKOCYTES.

Niu EM, Neal RM, Pierce VK, Sherman MR
(c/o Sherman) Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Steroid Biochem; 15:1-10 1981

Effects of molybdate on the apparent quantity and/or structure of the cytosol receptors for progestins and estrogens in human breast tumors, progestins in benign and malignant uterine endometrium, and glucocorticoids in normal lymphocytes and leukemic cells were studied. Estrogen receptors (ER) were labeled with [6,7-3H]-estradiol, glucocorticoid receptors with [6,7-3H]-triamcinolone acetonide (TA), progestin receptors (PR) with [17alpha-methyl-3H]-promegestone (R5020), and serum corticoid-binding globulin with [4-14C]-cortisol. For kinetic studies, the control solutions (-Mo) were made 30 milli (m)M in KCl, so that they had the same conductivity as those containing 20 mM Na2MoO4 (Mo). In the -Mo samples labeled with R5020, the specific binding was max between 1 and 2.5 hr, but declined to 54% of this value by 6.5 hr. In the Mo samples labeled with either lower or higher progestin concentrations, at least 92% of the max binding persisted after 6.5 hr; indicating that molybdate inhibits many but not all of the receptor-degrading processes in breast tumor (BT) cytosols. Results of gel filtration of PR and ER in BT and uterine specimens indicated that all of these receptors appear to exist in the same discrete form in hypotonic Mo buffers, regardless of the class of steroid, species, tissue, or state of health or malignancy. Steroid-binding specificity and ultracentrifugal analyses of molybdate stabilized receptors showed that the significant inhibition of progestin binding to PR by the synthetic glucocorticoid TA paralleled the inhibition detected in unfractionated Mo cytosol. Comparison of molecular parameters indicated mol wt of approx 310,000, an axial ratio of 11, and that the molecular architecture of receptors is highly conserved in a wide range of mammalian tissues. (55 Refs)

77. STUDIES ON NUCLEAR ESTRADIOL RECEPTORS IN HUMAN MAMMARY CARCINOMAS.

O'Connell M, McDonnell L, Duffy MJ
(c/o Duffy) Nuclear Medicine Dept., St. Vincent's Hosp., Dublin 4, Ireland
Clin Chim Acta; 119(3):285-289 1982

It is known that 50-70% of human primary mammary carcinomas possess cytoplasmic estradiol receptors (CER) and that over 5x as many CER- as non-CER-carcinomas respond to hormone manipulative therapy. This study demonstrates that 59% of CER- and 24% of non-CER carcinomas possess nuclear estradiol receptors (NER), whose presence should be a better indicator of amenability to this therapy. The correlation between CER and NER is r = 0.55 (p = 0.0001, n = 92). NER does not correlate with tumor cellularity, size, histological type, presence/absence of axillary node metastases, or cytosol levels of either total estrogens or progesterone. Presence or absence of NER does not alter the total cytosol estrogens median or the cytosol progesterone mean level. The percentage of tumors with over 25 fmol NER receptor/g wet weight decreases as the histologic tumor grade or stage increases, but not in a statistically significant manner. The significance of these findings is discussed in relation to recent literature on NER and CER, and rests upon results of ongoing clinical studies. (13 Refs)

78. RECEPTORS OF STEROID HORMONES IN HUMAN BREAST CANCERS.

Bassalyk LS, Murav'eva NI, Kuz'mina ZV, Smirnova KD, Vishniakova VV
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (12):19-23 1981

Prognostic value of the levels of steroid hormone receptors was studied in 64 patients (24-85 yr old) with primary breast cancer. Tumor specimens obtained at surgery were assayed for the presence of estrogen receptors (ER), progesterone receptors (PR), and glucocorticoid receptors (GR). The ER level ranged from less than 10 femtomoles/mg (fmoles/mg) in 35% of the patients, to 10-50 fmoles/mg in 41% and 51-300 fmoles/mg in 24%. The percent of ER-positive tumors in postmenopausal women was higher than that in premenopausal women. Positive correlation between the ER level and the efficacy of postoperative hormonal therapy was observed in 77% of the patients. The PR level in postmenopausal women was also higher than that in premenopausal women. The level of GR in pre- and postmenopausal women was 21 and 17 fmoles/mg, respectively. Preoperative hormonal therapy did not affect the level of ER and PR, while preoperative radiotherapy and chemotherapy reduced significantly the ER and PR levels. (9 Refs) (In RUS)

79. THE EFFECTS OF A SECOND SPECIFIC ESTROGEN BINDING SITE ON ESTROGEN RECEPTOR QUANTITATION IN HUMAN BREAST CANCER CYTOSOL.

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Dept. Pathology, Baylor Coll. Medicine, Houston, TX, 77030
J Steroid Biochem; 15:383-386 1981

The quantity of estrogen receptors (ER) in five pools of human breast cancer (HBC) tissue was determined by saturation analysis over a full or abbreviated range of ligand concentrations to determine how much type II estrogen binding site (II EBS) might affect the quantitation of ER in HBC cytosol. Results indicate that saturation analysis (SA) over a wide range of ligand values is an acceptable met hod to quantitate ER accurately. SA over a limited range of ligand concentrations does not allow the resolution or even detection of two-component binding systems. Use of a dextran-coated charcoal-based analytical system may not afford protection against error since it does not completely strip ligand from II ESB at a ligand concentration of 40 nanoM. (15 Refs)

80. ESTROGEN SULFURYLATION AS AN ALTERNATIVE INDICATOR OF HORMONE DEPENDENCE IN HUMAN BREAST CANCER.

Pewnim T, Adams JB, Ho KP
Sch. Biochemistry, Univ. New South Wales, Sydney, N.S.W. 2033, Australia
Steroids; 39(1):47-52 1982

Estrogen receptor (ER) levels, formation of 3'-phosphoadenosine-5'phosphosulfate (PAPS), and sulfate transfer to estradiol-17beta, have been determined in 62 human primary carcinoma cytosol preparations. While no differences between ER positive and ER negative tumors were found in the synthesis of [35S]PAPS, formation of estradiol-3-[35S]sulfate catalyzed by estrogen sulfotransferase was significantly higher in ER positive tumors [84 -10 (mean - S.E.M.) vs 32 -9 pmole estradiol-3-sulfate per mg protein per 2 hr for ER positive and ER negative tumors, respectively, p less than 0.02]. By choosing a discriminating value for estrogen sulfurylation of 40 pmole per mg protein per 2 hr, then 16/19 (84%) of the ER negative tumors were below this point. Since previous data had shown that 20/23 (87%) progesterone receptor negative tumors were also below this value, an alternative simple method, having a high potential for the evaluation of hormone responsiveness in mammary cancer, is suggested. (Author abstract) (7 Refs)

81. STEROID RECEPTORS IN MAMMARY CANCER.

Stojkovic RR
Zavod za opcu patolosku fiziologiju, Klinickog bolnickog centra u Zagrebu, Zagreb, Yugoslavia
Libri Oncol; 10(2/3):313-316 1981

Steroid receptors were determined in 500 patients with mammary cancer (MC). Primary MC was found in 434 patients, and 66 had metastasizing (ME) MC. Results of estrogen receptors in cytoplasm (ERc) were positive in 232 patients with primary MC and in 30 with ME MC. ERc and progesterone receptors (PgR) were determined in 315 patients, 33% of the patients had both ERc and PgR. Twenty-one percent of the patients had ERc only, while 14% had PgR only. Number of tumors containing PgR increases with increasing amount of ERc. The amount of ERc was increasing with the age of the patients. PgR in ERc tumors was approx the same before or after the menopause. ERc, PgR, and estrogen receptors in nucleus (ERn) were determined in the 97 MC patients. ERn was found in 37% of the patients, increasing to 66% in ERc. If ERc and ERn were positive, PgR was found in 90% of the patients; but when ERc was negative and ERn positive, PgR was found in 83%; when both (ERc and ERn) were negative, PgR was found in only 18% of the patients. Number of tumors containing PgR increases with increasing amount of ERc without relationship in their amounts, while amounts of PgR and ERn were significantly and positively correlated. Possible relationship of the three steroid receptors and success of hormonal therapy were discussed. (14 Refs) (In SCR)

82. STEROID RECEPTORS AS PROGNOSTIC INDICATORS IN PATIENTS WITH MAMMARY CANCER.

Bulic N, Budisic Z, Naranck P, Stojkovic R, Kubovic M, Gamulin S, Kosovel E, Martinac P, Montani Dj, Unusic J
Zavod za klinicku onkologiju i radioterapiju, Medicinski fakultet Sveucilista u Zagrebu, Zagreb, Yugoslavia
Libri Oncol; 10(2/3):317-321 1981

Estrogen receptors (ER) and progesterone receptors (PgR) were determined in 205 patients with mammary carcinoma. Twenty one percent of the patients were in Stage I, 61% in Stage II, and 18% in Stage III. Possible response to therapy was rated R for the patients with tumors containing ER greater than 100 femtomoles (fmol)/mg protein (pr) or ER greater than 3 fmol/mgpr and with PgR greater than 20 fmol/mgpr, R for the patients with ER between 3-100 fmol/mgpr, and PgR- or ER- and PgR greater than 20 fmol/mgpr, and R- for the remaining patients. The 113 patients in Stage I and in Stage II were evaluated for 18 mo after surgery; of the 36 patients rated R none had relapse; of the 20 patients rated R, 8/20 had relapse, and three of them died; and of 57 rated R-, 12/57 had relapse, and 5 of them died. The 94 patients in Stage I and Stage II were evaluated for 24 mo after surgery; of the 25 patients rated R, 2 had relapse, and 1 of them died; of the 19 patients rated R, 9 had relapse, and 3 of them died; and of the 50 patients rated R-, 17 had relapse, and 9 of them died. Discrepancy in results between R and R- could be due to adjuvant chemotherapy administered in higher percentage to the patients rated R-. Patients with low or negative values of the steroid receptors should be considered at high risk. (11 Refs) (In SCR)

83. SPECIFIC PROTEIN SYNTHESIS REGULATED BY ESTROGEN IN HUMAN BREAST CANCER.

Edwards DP, Adams DJ, McGuire WL
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J Steroid Biochem; 15:247-259 1981

Specific protein synthesis regulated by estrogen was studied in MCF-7 human breast cancer cells. Results for effects of estradiol on the pattern in protein synthesis, specificity of antiestrogen pretreatment, time course, estrogen dose response and hormone specificity of 24,000 mol wt (24k) stimulation, relationship between nuclear estrogen receptors and 24k stimulation, identity of 24k protein, two-dimensional electrophoresis, and estradiol stimulation of specific messenger RNA activity, are presented. Results indicate that specific proteins stimulated by estrogen in MCF-7 cells may prove to be suitable markers to study whether estrogens regulate expression of specific genes in breast cancer cells. (43 Refs)

84. OESTROGEN-INDUCED PROTEINS IN BREAST CANCER.

Vignon F, Capony F, Garcia M, Veith F, Westley B, Rochefort H
Unite d'Endocrinologie cellulaire et moleculaire, INSERM U 148 60, rue de Navacelles, F 34100 Montpellier, France
Ann Endocrinol (Paris); 42(4/5):327-332 1981

Estrogen-induced intracellular, secreted or membrane proteins are described. In breast cancer, the biosynthesis of progesterone receptors is stimulated by estrogens. Measurement of estrogen and progesterone receptors allows the prediction of hormone-dependence in the 80% of cancers that would benefit from hormone therapy. Progesterone receptors are stimulated by estrogens in hormone-independent tumors and by estrogen antagonists in hormone-sensitive tumors. Estrogens have been found to stimulate the synthesis of two proteins, with molecular wt of 24,000 and 36,000 daltons, in cells whose growth is blocked by estrogen antagonists. Production of cellular proteins C1, C2, and C3 (molecular wt 50-160 kilodaltons) is stimulated by estrogens. Some enzymatic activities in MCF7 cells are regulated by estrogens. A 46,000 dalton mol wt protein has been found in estrogen receptor-positive tumor cells which is not found in normal cells. Implications of these proteins for cancer therapy are discussed. (22 Refs) (In FRE)

85. INSULIN RECEPTORS IN HUMAN CANCER.

Benson EA, Holdaway IM
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Br J Cancer; 44(6):917-920 1981

A variety of human cancers were tested for specific receptors for insulin. Sixty-seven tissue samples (40 tumors, 24 fat, 3 muscle) were obtained during surgery were homogenized; the pellet contained receptors for prolactin and insulin. The insulin-binding assay was performed using porcine unlabeled and insulin labeled with 125I using chloramine-T. Specific binding was measured using Scatchard analysis. All specific binding values were adjusted to a membrane-protein concentration of 3.0 mg/ml; range of values found was 0.5-5.0 mg/ml. Significant insulin binding was detected in all tumor specimens except one breast-tumor sample which had a low yield of membrane protein of 1.5 mg/ml compared to an av value of 33.1 mg/ml. 125I-insulin binding to different types of tumor was compared with insulin binding to normal placenta, fat and muscle. Degradation of 125I-insulin by membranes from normal and tumor tissue was compared in one specimen of colon carcinoma. Little difference was detected in the rate of insulin degradation. Rate of degradation of labeled insulin also appeared similar in different types of tumor (colon, stomach, and breast). Affinity of binding decreased with increasing receptor occupancy. Apparently insulin receptors in normal cells are preserved during malignant transformation. However, other studies have shown that tumors can also synthesize ectopic hormone receptors. Results suggest that insulin binding is a common property of human cancer, and that insulin may help maintain or stimulate the growth of human tumors. (13 Refs)

86. THREE RADIOLIGANDS COMPARED FOR DETERMINING CYTOPLASMIC ESTROGEN-RECEPTOR CONTENT OF HUMAN BREAST CARCINOMAS.

Pieslor PC, Gibson RE, Eckelman WC, Oates KK, Cook B, Reba RC
(c/o Eckelman) Radiopharmaceutical Chemistry, George Washington Univ. Medical Center, 2300 I St. NW, Washington, DC, 20037
Clin Chem; 28(3):532-537 1982

We compared three radioligands for use in a cytoplasmic estrogen-receptor assay, using pooled cytosol from human breast adenocarcinomas. The estrogen receptor content was determined in vitro by a dextran-coated charcoal method involving a 4-hr incubation with and without diethylstilbestrol. Tritiated moxestrol failed to come to equilibrium in 4 hr, thereby preventing the use of conventional one-component Scatchard analysis. The use of 125I-labeled estradiol resulted in a higher estimate of estrogen-receptor concentration than that obtained with use of tritiated estradiol. This overestimation was not corrected by Scatchard, double-reciprocal, or Woolf plots, or by two different methods of data analysis: least squares and 'robust.' An underestimation of the specific activity of iodoestradiol with respect to that of tritiated estradiol and an unrecognized second component of nonreceptor binding could explain this disparity. (Author abstract) (24 Refs)

87. 1,25-DIHYDROXYVITAMIN D3 RECEPTORS IN HUMAN EPITHELIAL CANCER CELL LINES.

Colston K, Colston MJ, Fieldsteel AH, Feldman D
(c/o Feldman) Div. Endocrinology, S-005, Stanford Univ. Sch. Medicine, Stanford, CA, 94305
Cancer Res; 42(3):856-859 1982

Specific, high-affinity cytosolic receptors for 1,25-dihydroxyvitamin D3 have been demonstrated in five human cancer cell lines. The cell lines were derived from tumors of breast, lung, cervix, and melanotic and amelanotic melanomas. Binding affinity (Kd) of the receptors for 1,25-dihydroxyvitamin D3 were all approx 0.2 nM, and receptor content ranged from 21 to 174 fmol/mg cytosol protein. The receptors from all five cell lines sedimented at 3.2S on sucrose density gradients and exhibited preferential affinity for 1,25-dihydroxyvitamin D3 compared to other vitamin D metabolites. (Author abstract) (28 Refs)

88. PRESENCE OF 1,25-DIHYDROXYVITAMIN D3 RECEPTORS IN ESTABLISHED HUMAN CANCER CELL LINES IN CULTURE.

Frampton RJ, Suva LJ, Eisman JA, Findlay DM, Moore GE, Moseley JM, Martin TJ
(c/o Eisman) Dept. Medicine, Univ. Melbourne, Repatriation General Hosp., Heidelberg, Victoria, Australia
Cancer Res; 42(3):1116-1119 1982

Receptors for 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] have been described in several human breast cancer cell lines and more recently in human melanoma. The presence of 1,25-(OH)2D3 receptor (1,25-DR) in two cultured breast cancer cell lines was associated with receptors for calcitonin, another hormone thought to have effects on calcium handling. Therefore, it seemed important to examine a range of established human cancer cell lines for the presence of receptors for 1,25-(OH)2D3 and calcitonin. Thirty-three cancer cell lines were examined. 1,25-DR was found to be present in 23 lines, while calcitonin receptors were not detected in any of them. the 1,25-DR from several cell lines sedimented at about 3.5S in sucrose density gradients, had the appropriate specificity for vitamin D metabolites, had Kds of 0.8 x 2.2 x 10(-11) M, and had receptor concentrations of 12 to 99 fmol/mg protein. Ten malignant melanoma and 9 colonic carcinoma lines constituted the largest groups of carcinoma cell lines, and 7 and 8, respectively, of these were 1,25-DR positive. The high frequency of 1,25-DR positivity in the cultured colonic carcinoma cells is quite different from the low frequency of 1,25-DR in primary colonic carcinomas. It was also interesting that both of two cell lines derived from patients who had had both bone metastases and malignant hypercalcemia were 1,25-DR positive. These various cell lines may provide useful models for the examination of 1,25-(OH)2D3 action in vitro. (Author abstract) (31 Refs)

89. SIGNIFICANCE OF PREGNANCY-ASSOCIATED ALPHA2-GLYCOPROTEIN (ALPHA2-PAG) IN PATIENTS WITH BREAST, GASTRIC AND COLORECTAL CANCER.

Shimizu Y, Oshima K, Nakano Y, Fujita M, Taguchi T
Div. Oncologic Surgery, Dept. Clinical Res., Res. Inst. Microbial Diseases, Osaka Univ., 3-1, Yamada-oka, Suita, Osaka 565, Japan
Biken J; 24(3):95-102 1981

Pregnancy-associated alpha2-glycoprotein (alpha2-PAG) levels were measured in human sera by a modification of Laurell's electroimmunoassay using rabbit anti-alpha2-PAG serum. Sera were obtained from healthy controls (32 males and 46 females), patients with benign breast diseases (55 cases), and patients with breast (82 cases), gastric (89 cases), or colorectal (22 cases) cancers. In healthy controls, the mean alpha2-PAG value for females was higher than that for males (p less than 0.05), so alpha2-PAG values for males and females were considered separately in this study. Serum alpha2-PAG levels in patients with benign breast tumors were almost the same as those of controls. In patients with primary breast and gastric cancer, alpha2-PAG levels were higher than those of controls (p less than 0.005) and tended to increase with progress of the disease. Raised alpha2-PAG levels decreased in these patients after curative surgery. These results show that serum alpha2-PAG is useful as a marker in both the initial diagnosis and follow-up of breast and gastric cancer. The reliability of alpha2-PAG as a tumor-associated marker was reinforced by comparison of the positive rates of the three parameters alpha2-PAG, cacinoembryonic antigen (CEA), and immunosuppressive acidic protein (IAP) in patients with breast and gastric cancer. (Author abstract) (22 Refs)

90. EXPRESSION OF MULTIMOLECULAR FORMS OF PYRUVATE KINASE IN NORMAL, BENIGN, AND MALIGNANT HUMAN BREAST TISSUE.

Ibsen KH, Orlando RA, Garratt KN, Hernandez AM, Giorlando S, Nungaray G
Dept. Biological Chemistry, California Coll. Medicine, Univ. California, Irvine, CA, 92717
Cancer Res; 42(3):888-892 1982

The levels of multimolecular forms of pyruvate kinase present in four normal human breast specimens, nine benign tissues, and 13 malignant breast carcinomas were determined. The different enzymatic forms were separated by isoelectrofocusing, quantitated photometrically, and characterized further by kinetic studies using phosphoenolpyruvate as the variable substrate in the presence of different effectors. A correlation between specific activity and malignancy was found. The mean specific activities (- S E) of the normal, benign, and malignant tissues were: 0.078 -0.006, 0.36 -0.072, and 3.50 -0.696 IU/mg protein, respectively. A form of pyruvate kinase with an isoelectric point (pI) of 7.0 predominated in the breast tissues. The properties of this form were consistent with it being the K4 isozyme, known to be widely distributed in mammalian tissues. Higher pI forms were also found. The M4 isozyme, expressed by normal muscle and brain, has a pI value similar to the highest pI form found in the breast tissues. Therefore, the pI data alone suggest that the breast specimens also express some M-type subunits. This conclusion was not supported by the kinetic data. The higher pI forms are thought to be a posttranslationally modified K isozyme. Although this modified form is found in normal specimens, it seems more prevalent in neoplasms. (Author abstract) (19 Refs)

91. ESTROGEN RESPONSIVE CREATINE KINASE IN NORMAL AND NEOPLASTIC CELLS.

Kaye AM, Reiss N, Shaer A, Sluyser M, Iacobelli S, Amroch D, Soffer Y
Dept. Hormone Res., Weizmann Inst. Science, Rehovot, Israel
J Steroid Biochem; 15:69-75 1981

Estrogen-responsive creatine kinase (CK) brain type (BB) activity was compared during ontogeny of the Wistar rat uterus, in the human menstrual cycle and in GR mouse and human mammary tumors. Uterine CK increases in specific activity by 4.5-fold between 2 and 26 days of postnatal period in the rat; a decrease to 73-93% of the value at day 2 was found, at day 26, for phosphoglycerate kinase, phosphoglycerate mutase and enolase; the specific activity of pyruvate kinase increased by approx 50%. Specific activity of CK in adult rat uterus rose to nearly peak value by proestrus and reached max on the day of estrus. In human endometrial curettage samples a constant av activity 0.9 units/mg protein of CK was maintained until late luteal phase when increase in activity was observed (1.6 units/min/mg protein). CK activities of GR mouse mammary tumors during progression from hormone dependence to independence showed peak values in some lines; av value was near 0.6 micromole/min/mg protein. GR tumors were observed to undergo a switch in proportions of BB-estrogen induced and muscle type (MM)-non-estrogen responsive CK isozymes in intermediate generations, resulting in equal proportions of the two isozymes or a preponderance of the MM isozyme in later generations. Normal human breast and breast tumors contain both CK isozymes. Stimulation by estrogen of CK activity in normal breast tissue suggests the possibility that an increase induced in vitro, in the activity of BB of CK may provide a direct test for estrogen responsiveness of human breast tumor. (31 Refs)

92. COMPARISON BETWEEN BIOCHEMICAL AND HISTOCHEMICAL ASSESSMENTS OF PEROXIDASE ACTIVITY IN RAT MAMMARY TUMOURS.

Penney GC, Hawkins RA
Edinburh and S.E. Scotland Regional Blood Transfusion Service, Royal Infirmary Edinburgh, Edinburgh, EH3 9YW, Scotland
Histochem J; 13(6):983-988 1981

The endogenous peroxidase content of 26 'hormone-dependent' (induced by 7,12-dimethylbenz(a)anthracene) and 16 'hormone-independent' (transplantable) rat mammary tumors was assessed by means of a biochemical (guaiacol) assay on tumor extracts and by means of a histochemical (diaminobenzidine) technique on frozen sections of the same tumors. In the guaiacol assay, av peroxidase activity was 3.75 units/g for the hormone-dependent tumors compared to 0.26 units/g for the hormone-independent tumors (p less than 0.01). By the histochemical technique, with diaminobenzidine staining of the same tumors, peroxidase was detectable in 94% of hormone-independent tumors but in only 54% of hormone-dependent tumors. There was no direct correlation between the results of the two methods. The study indicates, that in these rat mammary tumors, histochemical estimates of peroxidase activity based on the diaminobenzidine reaction do not reflect the same tissue properties as biochemical estimates based on the guaiacol reaction after tissue disruption. (9 Refs)

93. SECRETION OF A THIOL PROTEINASE FROM MOUSE MAMMARY CARCINOMAS AND ITS CHARACTERIZATION.

Recklies AD, Mort JS, Poole AR
Joint Diseases Lab., Shriners Hosp. Crippled Children, Montreal, Quebec H3G 1A6, Canada
Cancer Res; 42(3):1026-1032 1982

Spontaneous mammary tumors from C3H/HeJ mice and transplants established from mammary tumors were investigated for their capacity to secrete thiol-dependent proteinase activity in organ culture explants. More activity was detected in culture media from spontaneous tumors than from transplanted spontaneous tumors. The accumulation of thiol proteinase in the culture medium was inhibited by cycloheximide, hydrocortisone, and aldosterone, but not by estradiol or the peptide hormones insulin or prolactin. The thiol proteinase is similar in enzymic properties to lysosomal cathepsin B, but its physical properties are different. It is stable to alkaline pH, has a larger molecular size on gel filtration (relative MW 39,000), and shows a different isoenzyme pattern to liver cathepsin B on analytical isoelectric focusing. The characteristics of this thiol proteinase are very similar to an enzyme secreted from malignant human breast tumors. (Author abstract) (39 Refs)

94. ENHANCED SYNTHESIS OF BASEMENT MEMBRANE PROTEINS DURING THE DIFFERENTIATION OF RAT MAMMARY TUMOUR EPITHELIAL CELLS INTO MYOEPITHELIAL-LIKE CELLS IN VITRO.

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Exp Cell Res; 137(2):373-380 1982

Rama 25, an epithelial cell line obtained from a dimethylbenzanthracene-induced rat mammary tumor differentiates spontaneously in culture forming elongated myoepithelial-like cells. The elongated cells form multilayered ridge structures from which cultures of elongated cells, relatively uncontaminated by epithelial cells, can be obtained. By using immunofluorescence techniques, both the elongated cells and the cells in ridges, but not undifferentiated Rama 25 cells, have been demonstrated to synthesize three basement membrane proteins, laminin, type IV collagen, and fibronectin. The identity of these basement membrane proteins has been confirmed by immunoprecipitation. These proteins appear to be located in a fibrillar extracellular matrix. We suggest that the ability to synthesize basement membrane proteins by mammary epithelial cells in vitro on plastic is a characteristic of myoepithelial-like cells. (Author abstract) (20 Refs)

95. KERATIN-LIKE PROTEINS IN NORMAL AND NEOPLASTIC CELLS OF HUMAN AND RAT MAMMARY GLAND AS REVEALED BY IMMUNOFLUORESCENCE MICROSCOPY.

Krepler R, Denk H, Weirich E, Schmid E, Franke WW

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Differentiation; 20(3):242-252 1981

Normal and neoplastic human breast tissue as well as lactating and nonlactating rat mammary glands and 7,12-dimethylbenz(a)-anthracene-induced mammary adenocarcinomas of rat, were examined by indirect immunofluorescence microscopy using guinea pig antibodies to human and bovine epidermal prekeratin and to cytokeratin polypeptide D from mouse hepatocytes. In normal mammary glands of both species, the antibodies raised against human and bovine epidermal prekeratins strongly stained ductal and myoepithelial cells, whereas antibodies to hepatic cytokeratin D revealed, in addition, fibrillar staining in cells of the alveolus-like terminal lobular units and in milk secreting cells of the rat. Our results show that all types of neoplastic and non-neoplastic epithelial cells of mammary gland of both species contain filaments of the cytokeratin type identifiable by immunologic reaction, if antibodies are used that recognize a broad range of epidermal and nonepidermal cytokeratins. Such broad range antibodies to keratin-like proteins provide adequate tools to identify and characterize neoplastic and non-neoplastic epithelial cells and to eliminate false negative immunocytochemical findings in tumor diagnosis. Our observation that in the same human carcinoma two cell types can be distinguished by their reaction with two different antibodies to cytokeratins from epidermis and liver, respectively, indicates that the cells of a given carcinoma can differ in their cytoskeletal composition, thus presenting further criteria for diagnostic differentiation. (48 Refs)

96. REGULATION OF CASEIN GENE EXPRESSION IN HORMONE-DEPENDENT MAMMARY CANCER.

Rosen JM, Supowit SC, Gupta P, Yu LY, Hobbs AA, Dao TL, Topp, Hilf
Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
Banbury Rep; 8:397-424 1981

Structure, organization, and expression of the casein gene (CG) family and the alpha-lactalbumin gene in the normal mammary gland, and altered regulation of CG expression and gene expression in general in hormone-dependent mammary cancer, were studied. Milk protein structural genes, hormonal regulation of milk protein messenger RNA accumulation in rat mammary gland organ culture, milk gene organization and chromosomal localization, CG expression in hormone-dependent mammary cancer, methylation patterns of the CG, DNA rearrangement in mammary tumors (MT), and expression of unique single-copy DNA sequences in 7,12-dimethylbenz(a)anthracene-induced MT are reviewed. New approaches may help explain the regulation of differentiated function in the normal mammary gland and deviation of the mechanisms in hormone-dependent breast cancer. (38 Refs)

97. MULTICENTRICITY AND BILATERALITY IN INVASIVE BREAST CARCINOMA.

Lesser ML, Rosen PP, Kinne DW
(c/o Rosen) Dept. Pathology, Memorial Hosp., 1275 York Ave., New York, NY, 10021
Surgery; 91(2):234-240 1982

Multicentricity and bilaterality are well-established characteristics of breast carcinoma, but little is known about the relationship of these variables with each other. This question was explored by analyzing the data pertaining to 880 women with invasive breast carcinoma. Patients with multicentric carcinoma had bilateral disease more often than those whose carcinoma was apparently limited to a single quadrant. Among women who had lobular carcinoma in situ coexisting with infiltrating duct carcinoma or infiltrating lobular carcinoma, bilaterality and multicentricity were significantly more common than they were among patients whose only lesion was infiltrating duct or medullary cancer. Other variables associated with bilaterality and multicentricity were degree of ductal differentiation, tumor size, nodal status, type of tumor margin, intensity of lymphoid infiltrate, and menstrual status. Age at diagnosis and estrogen receptors were related to bilaterality but not to multicentricity. The following variables proved to be unrelated to bilaterality and multicentricity: family history of breast carcinoma, height, wt, and parity. The data obtained in this study tend to support a conclusion that multicentricity and bilaterality are manifestations of similar factors involved in the neoplastic transformation of mammary gland epithelium leading to the development of breast cancer. (Author abstract) (14 Refs)

98. HORMONAL INDUCTION OF CASEIN GENE EXPRESSION LIMITED TO A SMALL SUBPOPULATION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY TUMOR CELLS.

Supowit SC, Rosen JM
(c/o Rosen) Dept. Cell Biology, Baylor Coll. Medicine, Houston, TX, 77030
Cancer Res; 42(4):1355-1360 1982

In the hormonally responsive 7,12-dimethylbenz(a)anthracene (DMBA)- or N-nitrosomethylurea (NMU)-induced mammary carcinomas, regulatory mechanisms have been altered such that these tumors retain their hormonal dependence for growth but possess only a limited ability to synthesize the mammary gland-specific milk proteins. Quantitation of casein mRNA levels revealed that very low levels of casein messenger RNA (mRNA) were expressed in both the DMBA- and NMU-induced tumors growing in virgin animals (0.1 to 0.4% of the maximally induced 8-day-lactating mammary gland). Growth of DMBA-induced tumors in pregnant rats and the treatment of NMU-induced tumor-bearing animals with thioproperazine indicated that the tumor casein mRNA levels were hormone inducible (3.4-and 2.1-fold for the DMBA- and NMU-induced tumors, respectively). However, casein mRNA levels were still only 1 to 2% of those found in the normal mammary gland under the same hormonal environment. Localization of the casein-synthesizing cells in the DMBA-induced tumors by peroxidase-antiperoxidase staining and a specific casein antiserum indicated that, in both control and hormone-treated tumors, the vast majority of cells (greater than 95%) were unable to synthesize casein. The hormonal induction of casein mRNA sequences could be correlated with an increase in the number of cells synthesizing casein, which appeared as small clusters of cells throughout the tumors. Therefore, the loss of hormone-regulated differentiated function in these tumors, which maintained hormone-dependent growth, suggests the presence of a defective regulatory mechanism beyond the level of the hormone-receptor complex. (Author abstract) (29 Refs)

99. MYOFIBROBLASTIC STROMAL REACTION IN RETRACTED SCIRRHOUS CARCINOMA OF THE BREAST.

Schurch W, Lagace R, Seemayer TA
Departement de Pathologie, Hotel-Dieu de Montreal, Montreal, Canada
Surg Gynecol Obstet; 154(3):351-358 1982

Thirty-four invasive and noninvasive primary carcinomas of the breast were examined by light microscopy, transmission electron microscopy and immunohistochemistry, the latter using an anti-actin antibody utilizing indirect immunofluorescence and immunoperoxidase. This study was designed to determine semiquantitatively the number and spatial relation of stromal myofibroblasts to the other components of carcinomas of the breast. The results were compared with several clinical and macroscopic features, including retraction of the skin and nipple, fixation of the neoplasm to adjacent tissue, consistency and aspect of the cut-surface of each carcinoma. Myofibroblasts were absent or equivocally present in noninvasive ductal, medullary and colloid carcinomas. They were most numerous in young mesenchymal stroma, areas corresponding to early stromal invasion or, more consistently, in the peripheral invasive cellular front of scirrhous carcinomas. The connective tissue adjacent to intraductal carcinomas lacked myofibroblasts, suggesting that stromal invasion of carcinomas is required to evoke a myofibroblastic stromal reaction. Myofibroblasts, which possess contractile and synthetic-collagen-properties, may contribute to the retraction phenomena and firm consistency of scirrhous carcinomas of the breast. The following mechanism is suggested to account for the retraction phenomena which characterize invasive ductal carcinomas of the breast. Contractile forces generated by myofibroblasts in the peripheral invasive cellular front are conveyed to the fascial septa, the Cooper's ligaments, which are connected with the fascia enveloping the breast. This fascia is attached superficially to the skin and deeply to the pectoral fascia. Contractile forces in or related to the carcinoma exert traction upon the fascial septa resulting in dimpling or retraction of the skin or nipple, or both; fixation to the underlying pectoral fascia; or fixation and decreased mobility of the neoplasm. Tissue retraction and exuberant collagen synthesis may represent an attempt to contain the neoplasm and retard access to vascular channels. (7 Refs)

100. MAMMARY TUMOR VIRUS DNA AS A MARKER FOR GENOTYPIC VARIANCE WITHIN HORMONE-RESPONSIVE GR MOUSE MAMMARY TUMORS.

Michalides R, Wagenaar E, Slyser M
Div. Virology and Endocrinology, Antoni van Leeuwenhoekhuis, The Netherlands Cancer Inst., 121 Plesmanlaan, 1066 CX Amsterdam, The Netherlands
Cancer Res; 42(3):1154-1158 1982

Mammary tumors of GR mice acquire extra mammary tumor virus (MMTV) DNA information within their DNA during tumor growth and development. These extra MMTV genes have been used by us as genotypic markers to investigate the heterogeneity of GR mammary tumors and their loss of hormone dependence during serial transplantation. Our studies reveal that the various subpopulations of cells within individual GR mammary tumors are characterized by differences in number and location of acquired extra MMTV DNA fragments. Losses of certain of these extra MMTV DNA fragments occur when mammary tumors become hormone independent, indicating a loss of hormone-dependent cells. The study of MMTV DNA markers also reveals that low levels of autonomous cells are already present in some hormone-dependent mammary tumors at an early stage of their development. The genotypic analysis strongly indicates that mammary tumor progression is not due to phenotypic adaptation but to clonal selection of the more aggressive sublines. (Author abstract) (20 Refs)

REVIEWS AND OTHER RELATED STUDIES

101. HORMONES AND BREAST CANCER.

Pike MC, Siiteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA. 90033
Banbury Rep 8: 491 pp., 1981.

Sessions held to discuss the relationship between hormones and breast cancer (BC) consisted of the following topics: review of BC epidemiology (as it relates to menarche, pregnancy, and menopause, body size and BC risk), endocrinology of women at risk of BC (hormone profiles in young women at risk of BC with analysis of ovarian function during theelarche, menarche, and menopause, and after childbirth, endocrine maturation during female puberty, reproductive endocrinology and BC in women, increased availability of serum estrogens in BC), review of studies attempting to establish endogenous hormones as important in human BC (estrogens, progesterone, and prolactin in human BC, prospective study of relation between thyroid function and BC, and abnormal plasma hormone levels in women with BC), in vitro studies of human breast tissue (hormonal regulation of human BC cells in vitro, prolactin, pituitary hormones, and BC, estrogen receptor assays in familial and nonfamilial BC), exogenous hormones and BC (epidemiological studies of the role of exogenous estrogens in BC etiology and hormone therapy), other exogenous factors and BC (epidemiological studies of mutagenicity of breast fluids and BC risk, diet and hormone metabolism in BC), hormones and genesis of progression of murine mammary tumors (ovarian steroid hormones, prolactin, growth hormone, insulin, pituitary and steroid hormones, pregnancy and lactation, neuroleptic drugs, and plasma prolactin analysis), and mechanism of hormone action (regulation of casein gene expression in hormone-dependent mammary cancer, control of estrogen-responsive tumor growth, and role of hormones in mammogenesis and carcinogenesis). (453 Refs)

102. ORAL CONTRACEPTIVES: VOLUME 5.

Briggs MH, Briggs M

Deakin Univ., Geelong 3217, Australia

Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews--Endocrinology, 331 pp., 1981.

Clinical trials, side effects, pharmacology, biochemistry, metabolism, and sociology of oral contraceptives (OC) are reviewed and discussed. Alternatives to the pill, new OC (combined oral products, OC for men), and older OC and therapeutic uses of contraceptive steroids are discussed, including their use in cancer therapy. Mortality and cardiovascular disease, hypertension, thrombosis, amenorrhea, and liver are affected by OC. Malformations and effect on offspring caused by diethylstilbestrol and other contraceptive steroids are reviewed. The role of OC in the genesis of breast, uterine endometrium, cervix, liver, and other neoplasms is discussed. OC may cause neurological, psychological, and other effects. Immunity and infection may be affected by OC. Mode of action, toxicology, contraceptive steroid metabolism, drug interactions, pharmacy, pharmacokinetics, and pharmacodynamics of OC are presented. Biochemistry and metabolism of OC are reviewed focusing on endocrinology (sex hormones, corticosteroids, protein hormones) and vitamins. (1179 Refs)

103. CELL SURFACE MODULATION IN MAMMARY CANCER.

Thomps[illegible]n K

Bruce Lyon Memorial Res. Lab., Children's Hosp. Medical Center, Oakland, CA, 94609

The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

Studies of the cell surface modulation which accompanies malignant transformation in mammary cancer are reviewed. Evidence for cell surface antigens (CSAs) of mouse and rat mammary tumors has not shown whether neoplastic transformation is associated with distinct tumor-specific antigens. Virus-induced mouse mammary tumors contain virus-specific antibodies, which are also present in normal mammary cells and nonmammary tissues. In rats with carcinogen-induced mammary tumors, the tumor loses an organ-specific antigen at the time of spontaneous dissemination. The experimental mammary tumors may also show gene derepression, which leads to the expression of abnormal differentiation antigens and/or fetal-type antigens. The tumors can acquire new CSAs not found in the tissue of origin and can acquire or lose CSAs already present in normal cells. Neoplastic transformation is a complex process, especially with regard to the cells which become neoplastic and the influence of host factors (genetic, hormonal, or immunologic). Interaction of these factors determines the malignant state. (283 Refs)

104. THE HANDBOOK OF CANCER IMMUNOLOGY: VOLUME 8: TUMOR ANTIGENS: STRUCTURE AND FUNCTION.

Waters H
NIH, Bethesda, MD
The Handbook of Cancer Immunology: Volume 8: Tumor Antigens: Structure and Function. New York, Garland STPM Press, 418 pp., 1981.

Structural and functional aspects of tumor antigens are reviewed. Mechanisms of reactions between lymphocytes and antigens are discussed. Characteristics of Ia antigens in mice and humans are presented and the significance of these antigens is considered. Histocompatibility antigens and tumor-associated antigens in plasma and urine are discussed and their diagnostic significance evaluated. Molecular structure and mechanisms of antibody-antigen interactions are outlined. Other topics include the use of cell membranes to assess phenotypic expression, masking of cancer-cell surface antigens, cell surface modulation in mammary cancer, antigen activation of T cells, assay and structure of carcinoembryonic antigens, induction of immune response to tumors induced by simian virus 40, and tumor-associated immunosuppressive serum proteins. Concentration and distribution of antigens are related to normal and pathological conditions. Discussion includes review of literature, presentation of original findings, and speculation on future research efforts. Converging and diverging viewpoints are expressed. (1659 Refs)

105. CELL SURFACE GLYCOPROTEIN MARKERS FOR NEOPLASIA.

Bhavanandan VP, Davidson EA
Dept. Biological Chemistry, Milton S. Hershey Medical Center, Hershey, PA, 17033
Methods Cancer Res; 19:53-105 1982

Glycoproteins that serve as cell surface markers of neoplasia are described biochemically, in relation to viral transformation, and for various animal and human cells, and the methods employed are reviewed. The animal tumors and derived cell lines discussed include the following: neuroblastoma, melanoma, ascites, hepatoma, mammary carcinoma, lung carcinoma, and leukemias and lymphomas. Glycoprotein cell surface markers in human cells are reviewed in relation to melanoma, mammary carcinoma, lung carcinoma, colon carcinoma, ovarian carcinoma, and neuroblastoma. Metabolic labeling, isolation, purification, mapping, and structural analysis techniques applied to glycoproteins are reviewed. Future studies in this field will probably take advantage of improved methods such as isoelectric focusing gels, lectin affinity chromatography, and monoclonal antibodies. Ultimately the metabolic and genetic origin of each macromolecule must be determined. In the meantime, glycoprotein cell surface marker studies may be expected to contribute to diagnostic and immunologic approaches to management of disease. (313 Refs)

106. PERSPECTIVES: IA SPECIFICITIES IN MOUSE AND MAN.

McKenzie IF, Sandrin MS, Parish CR
Dept. Medicine, Austin Hosp., Heidelberg, Victoria 3084, Australia
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

Two types of Ia antigen, in a limited tissue distribution, have been found in both mice and humans: a glycoprotein (Ia GLP; mol wt about 30,000) and a low mol wt glycolipid (Ia GLL). Both fractions are present on B-lymphocytes, a subpopulation of T-lymphocytes, a subpopulation of null cells, and macrophages. High levels of Ia GLL are also present in the serum; the concentration reflects the degree of T-cell activation. In both species, serum Ia GLL levels decline severely in the presence of a growing malignant tumor. Studies on the Ia antigen region of the major histocompatibility complex (MHC) of mice showed that the serum Ia GLL component is produced by Ia-T-lymphocytes (surface phenotype: Thy-1 Ly-1 Ly-2). Anti-Ia antibodies appeared in an animal rejecting a mammary carcinoma (A.TL) of Ia- surface phenotype, suggesting that the tumor may have secreted Ia antigens. These Ia molecules (possibly GLL) might interact with other molecules (either Ia GLL or GLP), leading to the suppression of host GLL production. These phenomena may be related to the altered cell surface GLL patterns observed in tumors. The I region of the MHC and the Ia antigens are probably involved in the immune response to tumors, as they seem to be involved in all or most immune reactions. It is suggested that the Ia GLL may play a particularly important role in oncogenesis. (194 Refs)

107. THE MASKING OF CANCER CELL SURFACE ANTIGENS.

Codington JF
Dept. Biological Chemistry, Harvard Medical Sch., Massachusetts General Hosp., Boston, MA, 02114
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

One major type of tumor antigen masking at tumor cell surfaces involves the masking of cryptantigens by sialic acid (SA) residues in terminal positions on carbohydrate chains. This may be involved in escape and control mechanism. Immunotherapy using neuraminidase can be used to expose SA-masked cryptantigens. Another type of tumor antigen masking at tumor cell surfaces involves a steric hindrance phenomenon caused by large endogenous glycoprotein (GLP) molecules. This may be involved in tumor allotransplantability and dissemination. The characteristics of GLPs which may be involved in antigenic masking of mouse and rat ascites mammary carcinomas are discussed. It is possible that mammalian tumor cells may utilize some of the protective mechanisms found in bacterial, parasitic, or mycoplasma infections. (133 Refs)

108. THE USE OF CELL MEMBRANES TO ASSESS PHENOTYPIC EXPRESSION.

Ceriani RL
Bruce Lyon Memorial Res. Lab., Children's Hosp. Medical Center, Oakland, CA, 94609
The Handbook of Cancer Immunology: Volume 8- Tumor Antigens: Structure and Function. Waters H, ed. New York, STPM Garland Press, 418 pp., 1981.

The specificity, distribution, properties, and levels of expression of milk fat globule membrane antigens in human and mouse mammary epithelial cells are discussed. When more is known about these 'antigens' cell surface expressions at the molecular level, they can be used to study cell-cell interactions, tissue invasiveness, and the dissemination of mammary neoplasms. It is emphasized that the term 'tumor antigens' is inappropriate for components that are normally expressed in an earlier stage of differentiation, which reappear in neoplastic cells. Neoplastic transformation leads to a protean instability of the antigenic phenotype. The appearance of early differentiation components and the gradual disappearance of the mature components seem to be strictly linked. Further research is needed to improve the culture of human breast epithelial tissues and identify their mammary epithelial origin and particularly their neoplastic phenotype. Normal mammary epithelial cells grow readily in vitro, but neoplastic cells do not. (88 Refs)

109. THE PLASMA MEMBRANE AS AN ADDITIONAL LEVEL OF STEROID-CELL INTERACTION.

Nenci I, Fabris G, Marzola A, Marchetti E
Istituto di Anatomia e Istologia Patologica, Uni. Ferrara, 44100 Ferrara, Italy
J Steroid Biochem; 15:231-234 1981

The occurrence of sites of interaction additional to specific classical receptors is discussed with special regard to their possible role in the cell economy. Vital cell suspensions freshly obtained from human breast tumors without any enzymatic or chemical pretreatment were used as the target-cell substratum. The cell plasma membrane represents an additional level of steroid-cell interaction and the properties of the surface binding sites are in accordance with the belief that multiple binding sites for steroid hormones occur in target cells. (12 Refs)

110. SEX-STEROID RECEPTORS IN MALIGNANT TUMORS.

Saez S
Centre Leon Berard, 28, rue Laennec, F 68373 Lyon Cedex 2, France
Ann Endocrinol (Paris); 42(4/5):306-314 1981

Relationships among steroid receptors and carcinogenesis, tumor growth, and cancer therapy are reviewed. Steroids favor the development of cancer through the stimulation of the growth of epithelium particularly in the breast, endometrium, and prostate gland. Disequilibration of hormones and hormone receptors metabolism appears to be related to carcinogenesis. Estrogen and progesterone receptors are discussed in relation to breast cancer. The development of vaginal cancer from ectopic epithelial cells following diethylstilbestrol exposure is described. Appearance of androgen and estrogen receptors in the colon following treatment with carcinogenic agents indicates that carcinogens themselves are related to the appearance and increase of hormone receptors. The clinical significance and the therapeutic implications of the presence of hormone receptors in breast, endometrium, and prostate is discussed. The exact content of receptors in a tumor is determined in part by the structure of the tissue and number of epithelial cells present. Cancer development seems to depend on the levels of receptors. The presence of hormone receptors in other cancers is considered. (28 Refs) (In FRE)

111. STEROID RECEPTORS IN BREAST CANCER.

Cowan K, Lippman M
Medical Breast Cancer Section, Medicine Branch, NCI, NIH, Building 10, Room 6B02, Bethesda, MD, 20205
Arch Intern Med; 142(2):363-366 1982

Progress in hormone action mechanisms, analysis of estrogen receptors (ER) and progesterone receptors (PR), ER and disease-free interval, and ER and response to cytotoxic chemotherapy (CCT) are reviewed. According to the current hypothesis regarding mechanisms of action, circulating steroid hormones are first taken up by target cells and subsequently bind to specific cytoplasmic receptor molecules. New protein synthesis that occurs in hormone-responsive cells results in changes in the cell phenotype. Reasons for the lack of a perfect correlation between ER status and response to endocrine therapy are the instability of steroid receptors, heterogeneity of malignant cells, existence of numerous endocrine therapies that are ablative and additive, hormone-dependent and independent tumor cells, and the possibility of primarily nuclear location of ER sites and their undetectability in routine assays of cytoplasmic receptors. Patients with tumors that contain both ER and PR have the highest frequency of response (75-80%) to endocrine therapy. Explanations for apparent lack of complete correlation between the presence of PR and response to hormonal therapy are that the biopsy specimens were obtained during the luteal phase of the menstrual cycle and that some postmenopausal patients may actually have concentrations of endogenous estrogen that are insufficient to induce detectable increments of tumor PR activity. ER determination could aid in the selection of a subgroup of women with stage I primary breast cancer who might benefit from early aggressive adjuvant therapy. A definite role of ER status in selection of patients for CCT has not been established. (34 Refs)

112. THREE STUDIES IN PSYCHOSOMATIC MEDICINE REVISITED: A TRIBUTE TO THE PSYCHOBIOLOGICAL PERSPECTIVE OF HERBERT WEINER.

Katz JL

Dept. Psychiatry, Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, NY, 10467

Psychosom Med; 44(1):29-41 1982

Psychoendocrine considerations in cancer of the breast, psychosomatic aspects of gout, and the psychobiology of anorexia nervosa are reviewed, focusing on the importance of mediating variables, the differences among predisposing, precipitating, and sustaining factors in illness, the nature of the transduction of experience in the developing CNS, and the multiplicity of ways in which regulating systems can be disrupted to produce the same pathologic endpoint. (34 Refs)

113. ALTERATIONS IN THE GENE EXPRESSION IN TUMORS.

Gamulin S

Zavod za opcu patolosku fiziologiju Medicinskog fakulteta, Klinicki bolnicki centar, Kispaticeva 12, Zagreb, Yugoslavia

Lijec Vjesn; 103(4/5):201-203 1981

Alterations of gene expression in tumors are discussed. Relationship of cytoplasmic (ERc) and nuclear estrogen receptors (ERn) and progesterone receptors (PgR) in human breast cancer was studied in 97 females patients. PgR were correlated with the presence of ERn in more than 80% of the cases. Presence or absence of ERc had no influence on PgR. Significant correlation was observed between ERn and PgR, but no correlation was observed between these receptors and ERc. Presence of PgR in some ERn negative (ERn-) tumors indicates the possibility that PgR synthesis does not depend on the induction. Various combinations of receptors were observed in the studied tumors. In the ERc positive (ERc) group some of the tumors contained no ERn. Levels of endogenous estradiol appeared sufficient to induce PgR and the translocation of ERn and ERc. Forty percent of ERc tumors are nonresponsive to hormonal therapy. Eleven percent of ERc- tumors contain ERc-, ERn, and PgR, and they are responsive to hormonal therapy. Determination of ERn in the cell nuclei of breast cancer could help in identification of hormone resistant tumors with no ERc and defect mechanisms for receptor translocation. (24 Refs) (In SCR)

114. TRACE METALS AND DISEASES.

Yamane Y, Sakai K
Faculty Pharmaceutical Sciences, Chiba Univ., Yayoi-cho 1-33, Chiba 260, Japan

Yuki Gosei Kagaku Kyokai Shi; 39(11):1105-1113 1981

Trace metal diseases (eg acrodermatitis enteropathica and Menkes' kinky-hair disease), diseases that cause abnormalities in metabolism of essential trace metals (eg Wilson's disease, cystic fibrosis, and hemochromatosis), assays of trace metals in biological fluids as diagnostic or prognostic aids in patients with cancer, and toxic trace metals were discussed. There are many influences that trace metals have on cancer. For example, pernicious anemia often accompanies various serious types of cancer and is related to iron, copper, and cobalt. Most patients with bronchial or some other lung cancers or transverse colon cancer have decreased serum levels of zinc, but patients with breast cancer or melanoma do not have decreased levels of zinc. Patients with primary osteosarcoma have lower copper/zinc ratios than normal subjects, and patients with metastatic osteosarcoma have copper/zinc ratios higher than normal subjects, suggesting a way to differentiate the two types of osteosarcoma. Compared to normal subjects, patients with breast cancer have 6-7x higher levels of total iron in breast tissue, patients with lung cancer have one fifth of the normal level of total iron in lung tissues, and patients with cancer of the transverse colon have normal levels of total iron in the colon tissue. Other studies have indicated the carcinogenic potential of toxic trace metals. (63 Refs) (In JPN)

115. PROMISING AREAS OF CANCER RESEARCH.

Good RA, Day NK, Witkin SS, Fernandes G
Memorial Sloan-Kettering Cancer Center, New York, NY

Cancer- Achievements, Challenges, and Prospects for the 1980s, Proceedings of an International Conference held in New York, 14-16 September, 1980. Vol. 2, Memorial Sloan-Kettering Cancer Center New York, NY. Burchenal, J. H. and Oettgen, H. F., eds. (New York, Grune and Stratton), 944 pp., 1981.

Promising areas of cancer research are discussed. Manipulation of the immune system has altered the outcome of naturally occurring cancers in laboratory animals. Recent studies indicate the existence of more than one form of breast cancer, some of which are related to the murine mammary tumor virus which causes breast cancer in mice. Continued analysis of cellular and humoral immune responses in cancer and the diseases of aging should be rewarding. Immunologic approaches may contribute to treatment and prevention of common cancers. (89 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO MAN. SOME ANTINEOPLASTIC AND IMMUNOSUPPRESSIVE AGENTS.
Schmahl D
International Agency for Cancer Research, Lyon, France
IARC Mongr Eval Carcinog Risk Chem Hum 26: 411 pp., 1981.

2. BIOCHEMICAL TOXICOLOGY OF BENZENE.
Snyder R, Longacre SL, Witmer CM, Kocsis JJ, Andrews LS, Lee EW
Dept. Pharmacology, Thomas Jefferson Univ., Philadelphia, PA, 19107
Rev Biochem Toxicol; 3:123-153 1981

3. A REVIEW OF THE MUTAGENICITY OF CHROMIUM.
Hatherill JR
Toxicology, Sch. Public Health, Univ. Michigan, Ann Arbor, MI, 48109
Drug Chem Toxicol; 4(3):185-195 1981

4. HORMONES AND BREAST CANCER.
Pike MC, Siiteri PK, Welsch CW
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Banbury Rep 8: 491 pp., 1981.

5. ORAL CONTRACEPTIVES: VOLUME 5.
Briggs MH, Briggs M
Deakin Univ., Geelong 3217, Australia
Oral Contraceptives: Volume 5. St. Albans, VT, Eden Medical Research Inc., Annual Research Reviews--Endocrinology, 331 pp., 1981.

6. EPIDEMIOLOGICAL STUDIES OF THE ROLE OF EXOGENOUS ESTROGENS IN THE ETIOLOGY OF BREAST CANCER.
Kelsey JL, Bulbrook RD, Korenman SG, Siiteri PK, Henderson BE
Dept. Epidemiology and Public Health, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Banbury Rep; 8:215-228 1981

7. EFFECTS OF LONG-TERM EXPOSURE TO LOW LEVELS OF OZONE: A REVIEW.
Melton CE
Civil Aeromedical Inst., Federal Aviation Admin., Oklahoma City, OK, 73125
Aviat Space Environ Med; 53(2):105-111 1982

8. METABOLIC INTERACTIONS OF HYDROCARBONS WITH MAMMALIAN LUNG.
Smith BR, Bend JR
Lab. Pharmacology, Natl. Inst. Environmental Health Sciences, NIH, Research Triangle Park, NC, 27709
Rev Biochem Toxicol; 3:77-122 1981

9. REVIEW OF EXPERIMENTAL CARCINOGENESIS BY COMPOUNDS RELATED TO VINYL CHLORIDE.
Chu KC, Milman HA
NCI, Bethesda, MD, 20205
Environ Health Perspect; 41:211-220 1981

10. REVIEWS IN BIOCHEMICAL TOXICOLOGY.
Hodgson E, Bend JR, Philpot RM
North Carolina State Univ., Raleigh, NC
Rev Biochem Toxicol 3: 368 pp., 1981.

DIETARY FACTORS IN CARCINOGENESIS

11. ALCOHOL AND CANCER.
MacSween RN
Univ. Dept. Pathology, Western Infirmary, Glasgow, Scotland
Br Med Bull; 38(1):31-33 1982

12. THE TOXICOLOGY OF COCOA AND METHYLXANTHINES: A REVIEW OF THE LITERATURE.
Tarka SM
Life Sciences, Hershey Foods Corp., Corporate Technical Center, Hershey, PA
CRC Crit Rev Toxicol; 9(4):275-312 1982

13. IMPLICATIONS OF DIETARY FIBER BREAKDOWN IN THE HUMAN COLON.
Cummings JH, Stephen AM, Branch WJ
MRC Dunn Clinical Nutrition Centre, Old Addenbrookes Hosp., Cambridge, CB2 IQE, England
Banbury Rep; 7:71-81 1981

14. BILE SALTS AND OTHER CONSTITUENTS OF THE COLON AS TUMOR PROMOTERS.
Reddy BS, Tannenbaum SR, Montesano R, Correa P, Haenszel W, Wattenberg LW
Div. Nutrition, American Health Foundation, Naylor Dana Inst. for Disease Prevention, Valhalla, NY, 10595
Banbury Rep; 7:345-363 1981

15. MOLD PRODUCING CARCINOGENIC TOXINS IN FOOD PRODUCTS.
Preda N
Institutul de medicina si farmacie, Cluj-Napoca, Romania
Rev Chir [Oncol]; 20(1):1-9 1981
In RUM

16. THE MEANING OF CANCER 'DIETS'.
Jungi WF
Abt. f. Onkologie-Hamatologie, Medizinische Klinik C, CH-9007 St. Gallen, Switzerland
MMW; 124(2):26-28 1982
In GER

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17. RISK FACTORS FOR CERVICAL CANCER.
Hulka BS
Dept. Epidemiology, Rosenau Hall 201H, Univ. North Carolina, Chapel Hill, North Carolina, NC, 27514
J Chronic Dis; 35(1):3-11 1982

18. EPIDEMIOLOGY OF THE MOST FREQUENTLY OCCURRING TUMORS OF THE DIGESTIVE SYSTEM.
Naujoks-Heinrich S, Dolle W
Abteilung Innere Medizin I, Universitatsklinik, Otfried-Muller-Strasse 10, D-7400 Tubingen, W. Germany
Internist (Berlin); 23(1):1-9 1982
In GER

19. BLADDER CANCER.
Skrabanek P, Walsh A
Endocrine Oncology Unit, Mater Misericordiae Hosp., Dublin, Ireland
UICC Tech Rep Ser 60: 192 pp., 1981.

20. RECENT ADVANCES IN CANCER CYTOGENETICS.
Pogosiants EE
All-Union Cancer Res. Center, Moscow, USSR
Genetika; 17(12):2087-2099 1981
In RUS

21. CURRENT STATUS OF CYTOGENETIC STUDIES IN ANIMAL TUMORS WITH SPECIAL REFERENCE TO NONRANDOM CHROMOSOME CHANGES.
Sasaki M
Chromosome Res. Unit, Hokkaido Univ., Faculty Science, Sapporo 060, Japan
Cancer Genet Cytogenet; 5(2):153-172 1982

ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

22. ASBESTOS-RELATED DISEASES.
Casey KR, Rom WN, Moatamed F
Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):179-202 1981

23. NONASBESTOS FIBROUS MINERALS.
Lockey JE
Building 512, RMCOEH, Univ. Utah Medical Center, Salt Lake City, UT, 84112
Clin Chest Med; 2(2):203-218 1981

24. REVIEW OF EPIDEMIOLOGIC STUDY RESULTS OF VINYL CHLORIDE-RELATED COMPOUNDS.
Apfeldorf R, Infante PF
Office Carcinogen Identification and Classification, Health Standards, Programs, Occupational Safety and Health Admin. U. S. Dept. Labor, Washington, DC, 20210
Environ Health Perspect; 41:221-226 1981

25. CONCEPTS IN CAUSALITY: CHEMICALLY INDUCED HUMAN URINARY BLADDER CANCER.
Lower GM
Center Human Systems, Inst. Environmental Studies, Univ. Wisconsin, WARF Building, 610 Walnut St., Madison, WI, 53706
Cancer; 49(5):1056-1066 1982

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

26. MOLECULAR MECHANISM OF ADAPTATION OF CELLS TO LOW LEVELS OF CARCINOGENIC AGENTS.
Villani G
Laboratoire de Pharmacologie et de Toxicologie Fondamentales, CNRS, 205, route de Narbonne, 31078 Toulouse Cedex, France
Pathol Biol (Paris); 30(2):117-123 1982
In FRE

27. MIGHT CANCER BE A FAILED RESPONSE TO RENEGADE MITOCHONDRIA?
Hartung J
Dept. Anesthesiology, State Univ. New York, Downstate Medical Center, Brooklyn, NY, 11203
J Theor Biol; 94(1):173-178 1982

MODIFICATION OF CARCINOGENESIS

28. EFFECT OF GEROPROTECTORS ON CARCINOGENESIS.
Anisimov VN
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Usp Sovrem Biol; 92(3):455-472 1981
In RUS

29. RELATION OF NEUROLEPTIC DRUGS TO DEVELOPMENT AND GROWTH OF MAMMARY TUMORS.
Meites J, Aylsworth CF
Dept. Physiology, Neuroendocrine Res. Lab., Michigan State Univ., East Lansing, MI, 48824
Banbury Rep; 8:365-376 1981

30. THE ACTIONS OF INSULIN AS A HORMONAL FACTOR IN BREAST CANCER.
Hilf R, Siiteri PK, Shellabarger, Korenman SG, Rosen, Nandi
Dept. Biochemistry and Univ. Rochester Cancer Center, Univ. Rochester, Rochester, NY, 14642
Banbury Rep; 8:317-337 1981

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31. ONCOGENES.
Bishop JM
Univ. California, San Francisco, CA
Sci Am; 246(3):80-84,87-92,154 1982

32. HUMAN CANCERS AND HUMAN VIRUSES.
Waterson AP
Royal Postgraduate Medical Sch., London W12 0HS, England
Br Med J; 284(6314):446-448 1982

33. THE IMMUNOLOGY OF CANCER OF THE HEAD AND NECK WITH PARTICULAR REFERENCE TO ORAL CANCER.
Scully C
Univ. Dept. Oral Medicine and Pathology, Immunology Unit, Glasgow Dental Hosp., 378 Sauchiehall St., Glasgow G2 3JZ, Scotland
Oral Surg; 53(2):157-169 1982

METHODOLOGY IN CARCINOGENESIS RESEARCH

34. THE USE OF MAMMALIAN CELL MUTANTS TO STUDY THE MECHANISMS OF CARCINOGENESIS.
Trosko JE, Chang CC, Warren ST, Liu PK, Wade MH, Tsushimoto G
Dept. Pediatrics and Human Development, Michigan State Univ., Coll. Human Medicine, East Lansing, MI, 48824
Gann Monogr Cancer Res; 27:159-179 1982

35. BIOLOGICAL MONITORING IN THE IDENTIFICATION OF THE CANCER RISK OF INDIVIDUALS EXPOSED TO CHEMICAL CARCINOGENS.
Vainio H, Sorsa M, Rantanen J, Hemminki K, Aitio A
Inst. Occupational Health, Haartmaninkatu 1, SF-00290 Helsinki 29, Finland
Scand J Work Environ Health; 7(4):241-251 1981

36. A CRITICAL REVIEW OF BIOLOGICAL METHODS FOR THE DETECTION OF FUNGAL TOXINS IN FOODS AND FOODSTUFFS.
Watson DH, Lindsay DG
Food Science Div., Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London SW1P 2AE, England
J Sci Food Agric; 33(1):59-67 1982

37. PITUITARY AND STEROID HORMONES IN RADIATION-INDUCED MAMMARY TUMORS.
Shellabarger CJ
Medical Dept., Brookhaven National Lab., Upton, NY, 11973
Banbury Rep; 8:339-351 1981

38. ASPERGILLUS NIDULANS: SYSTEMS AND RESULTS OF TESTS FOR CHEMICAL INDUCTION OF MITOTIC SEGREGATION AND MUTATION. I. DIPLOID AND DUPLICATION ASSAY SYSTEMS. A REPORT OF THE U. S. EPA GENE-TOX PROGRAM.
Kafer E, Scott BR, Dorn GL, Stafford R
Dept. Biology, McGill Univ., 1205 Ave. Docteur Penfield, Montreal H3A 1B1, Canada
Mutat Res; 98(1):1-48 1982

OTHER REVIEWS IN CARCINOGENESIS

39. MATHEMATICAL MODELS OF THE CELL CYCLE WITH A VIEW TO TUMOR STUDIES.
Bertuzzi A, Gandolfi A, Giovenco MA
Centro di Studio dei Sistemi di Controllo e Calcolo Automatici del C.N.R., Via Eudossiana 18, 00184 Rome, Italy
Math Biosci; 53(3/4):159-188 1981

40. NEOPLASMS IN DOMESTIC ANIMALS: A REVIEW OF EXPERIMENTAL AND SPONTANEOUS CARCINOGENESIS.
Madewell BR

Section Clinical Oncology, Dept. Veterinary Surgery, Univ. California, Davis, CA, 95616

Yale J Biol Med; 54(2):111-125 1981

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AUGUST, 1982

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- FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER 3-17
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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PREVALENCE OF BREAST CANCER IN HUMAN POPULATIONS

1. IS BREAST CANCER INCIDENCE ON THE RISE IN SWEDEN?.

Mattsson B, Rutqvist LE, Wallgren A
Stockholm-Gotlands onkologiska centrums kansli, Stockholm, Sweden
Lakartidningen; 79(7):495-497 1982

The breast cancer incidence and mortality for Swedish women were analyzed on the basis of statistical data for birth cohorts. The age-standardized breast cancer incidence has increased by an av of 1.5%/yr during the period 1960-1977, while the mortality has remained practically unchanged. The incidence has increased in all birth cohorts at least beyond the age of 45 yr. The discrepancy between increasing incidence and practically constant mortality rate can be explained by earlier and more effective therapeutic intervention, diagnosis of increasing numbers of earlier cases with better prognosis, or by an apparent increase due to earlier diagnosis of already existing cases. Earlier diagnosis or an increase in the number of curable cases is the most acceptable explanation. Approx 63% of the women treated for breast cancer 40 yr ago already had lymph node metastases, while the corresponding percentage was only 40% during the late 60s. (7 Refs) (In SWE)

2. CANCER IN LIBERIA: A REVIEW OF CASES REGISTERED FROM THE LIBERIA CANCER REGISTRY 1973-1977.

Sobo AO
JFK Medical Center, P.O. Box 1973, Monrovia, Liberia
Cancer; 49(9):1945-1951 1982

Data from the Liberia Cancer Registry are reviewed for a 5-yr period. Information collected included name, age, sex, tumor site, and histologic diagnosis. Collection of accurate data was complicated by factors including inadequate diagnostic facilities, lack of documentation of patient age, and the tendency for more affluent patients to seek treatment abroad. During the first 5 yr of the registry 1,652 patients (766 men and 866 women) were registered. The total incidence of cancers was 22.5 cases/100,000 population. The incidence was fairly constant during the period, except for a decline in the last yr. Approx 10% of patients were of undetermined age. Among males the most common cancers included cancer of the liver (16.2% of cases), cancer of the prostate (11.0%), Hodgkin's disease (8.5%), Burkitt's lymphoma (8.2%), and cancer of the bladder (7.7%). Among females the most common cancers included cancer of the cervix (28.1% of cases), cancer of the breast (11.1%), cancer of the ovary (10.4%), cancer of the liver (5.4%), choriocarcinoma (4.9%), and Burkitt's lymphoma (4.2%). The frequency of lung cancer was low in both sexes, and skin cancers were less frequent than those reported in Senegal and the Cameroons. (18 Refs)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

3. DIET AND HORMONE PROFILES IN TEENAGE GIRLS IN FOUR COUNTRIES AT DIFFERENT RISK FOR BREAST CANCER.

Gray GE, Pike MC, Hirayama T, Tellez J, Gerkins V, Brown JB, Casagrande JT, Henderson BE
(c/o Henderson) Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, 2025 Zonal Ave., Los Angeles, CA, 90033
Prev Med; 11(1):108-113 1982

Findings on diet and possible breast cancer risk factors in adolescent girls in Chile (CH), Japan (JA), Papua New Guinea (PNG), and the United States (US) are presented. The 51 CH girls (mean age 17.0 yr), 50 JA girls (mean age 16.9 yr), and 68 PNG girls (mean age 17.7 yr) were from rural areas, and the 50 US girls (mean age 16.5) were all members of the same church. The subjects were postmenarchial with an av cycle of 26-32 days and had never been pregnant or used oral contraceptives or other medication known to influence sex hormone levels (SHL). Blood samples were to be collected in the morning not less than 30 min after the subject awakened on day 11 of the menstrual cycle; the condition was achieved for all girls except for 32% of CH girls. Obvious differences in body build among the subjects from the countries were noted. Dietary data and mean SHL are presented. The only significant differences were in urinary estriol and the urinary estriol ratio. The levels were considerably higher in PNG girls than in those from girls from the other three countries. Correlation coefficients were calculated to assess the relationship between anthropometric measurements, age, age at menarche, percentage of calories from fat, carbohydrate, and protein, and SHL within each country. No consistent relationship between SHL and any of the other factors were found. The anthropometric measurements and age at menarche were not related to the dietary variables within each country. According to the results, at least with diets leading to the same age at menarche, an increased percentage of calories from fat does not increase prolactin levels. (24 Refs)

4. DIET AND HORMONE LEVELS IN SEVENTH-DAY ADVENTIST TEENAGE GIRLS.

Gray GE, Williams P, Gerkins V, Brown JB, Armstrong B, Phillips R, Casagrande JT, Pike MC, Henderson BE
(c/o Henderson) Dept. Family and Preventive Medicine, Univ. Southern California, 2025 Zonal Ave., Los Angeles, CA, 90033
Prev Med; 11(1):103-107 1982

Differences in age at menarche and in plasma and urine hormone levels between meat eating and non-meat-eating Adventists were investigated. White girls (14-17 yr old) who had menstrual cycles 27-32 days in length, had never used oral contraceptives, had never been pregnant, did not take medication regularly, had no prior history of gynecological, endocrine, or neoplastic diseases, and were willing to have blood and urine specimens taken for hormone analysis were included in the study. Twenty-three girls who had never eaten meat on a regular basis (VE) and 26 who were eating meat, fish, or poultry at least weekly (NVE) completed a detailed questionnaire on dietary habits. Blood samples were collected between 30 min and 2 hr after arising on days 11 and 22 of the same menstrual cycle. VE and NVE girls did not differ in height, wt, or age at menarche. The relative amounts of protein, fat, and carbohydrates expressed as percentages of calories consumed by both groups were similar. The hormone levels were similar and no statistically significant differences were found. Risk from dying of breast cancer for California Seventh-Day Adventist women is approx 30% lower than that of the general population; the difference has been attributed to dietary habits. The hypothesis that meat consumption is a risk factor for breast cancer is questioned. (19 Refs)

5. ASSESSING HUMAN EPIDEMIOLOGIC DATA ON DIET AS AN ETIOLOGIC FACTOR IN CANCER DEVELOPMENT.

Enstrom JE
Sch. Public Health, Univ. California, Los Angeles, CA
Bull NY Acad Med; 58(3):313-322 1982

Assessment of the relationship between diet and cancer is reviewed. Epidemiology of cancer among human populations consists of randomized, controlled trials based on interpretation of naturally occurring phenomena. The strongest epidemiologic data relating diet to cancer are geographic correlations between such factors as per capita fat consumption and age adjusted colon and breast cancer rates. Weaknesses exist in such correlation: large variation in colon cancer rates occurs within the United States (US), even when fat intake remains constant. Studies of Japanese who migrate from Japan to the US provide another form of epidemiologic evidence for a correlation between diet and cancer. Japanese emigrants in the US have increased rates for colon and breast cancer as compared to native Japanese; such selective use of epidemiologic data is partially contradicted by other data which indicate that the overall total cancer rate among Japanese Americans remains unchanged, with a total death rate lower than that of native Japanese. Specific populations which maintain diets different from the average American diet are discussed, using as examples Mormons and Mexican Americans. No data has demonstrated any specific relationship between diet and cancer rate. (26 Refs)

6. BIAS AND THE ASSOCIATION OF MAMMOGRAPHIC PARENCHYMAL PATTERNS WITH BREAST CANCER.

Boyd NF, O'Sullivan B, Campbell JE, Fishell E, Simor I, Cooke G, Germanson T
Dept. Medicine, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario, Canada
Br J Cancer; 45(2):179-184 1982

We have carried out a case-control study to evaluate the association between Wolfe's mammographic patterns and the risk of breast cancer, and to examine the influence of control selection and the radiologist who reads the films upon the results obtained. Mammograms of the non-cancerous breast of 183 women with unilateral breast cancer were compared with mammograms from two age-matched control groups: a group of asymptomatic women attending a screening center, and a group of symptomatic women referred for the diagnostic evaluation of suspected breast disease. Films were arranged in random sequence and independently classified by three radiologists. A strong and statistically significant association was found between mammographic dysplasia and breast cancer when controls from the screening center were compared to cases, but not when cases were compared to women referred for the diagnostic evaluation of breast disease. This result appears to arise in part because of an association between symptoms of benign breast disease and mammographic dysplasia, and suggests that some previous negative studies of the association of mammographic patterns with breast cancer may have arisen from the inclusion of symptomatic subjects as controls. (Author abstract) (23 Refs)

7. MAMMOGRAPHIC SIGNS AS RISK FACTORS FOR BREAST CANCER.

Boyd NF, O'Sullivan B, Campbell JE, Fishell E, Simor I, Cooke G, Germanson T

Dept. Medicine, Princess Margaret Hosp., 500 Sherbourne St., Toronto, Ontario, Canada

Br J Cancer; 45(2):185-193 1982

We have carried out a case-control study to examine the relationship between mammographic signs and breast cancer. The mammographic signs assessed were prominent ducts and dysplasia. The cases were a group of 183 women with histologically verified unilateral breast cancer. The controls were a group of women attending a screening center. Cases and controls were individually age-matched. Mammograms from the non-cancerous breast of the cases were randomly assembled with those of the controls and classified by three radiologists without knowledge of which films were from cases and which from controls. Mammographic dysplasia was found to be strongly associated with breast cancer, particularly in women aged less than 50. Prominent ducts were only weakly associated with breast cancer. Multivariate analysis showed that the association between dysplasia and breast cancer could not be explained on the basis of other risk factors for breast cancer, and that classification of dysplasia discriminated more strongly between cases and controls than did classification of Wolfe's mammographic patterns. These results show that mammograms contain information about risk of breast cancer. Mammographic dysplasia is strongly associated with breast cancer, is present in a substantial proportion of patients with the disease, and may offer opportunities for prevention. (Author abstract) (27 Refs)

8. MAMMOGRAPHIC FEATURES OF THE BREAST AND BREAST CANCER RISK.

Brisson J, Merletti F, Sadowsky NL, Twaddle JA, Morrison AS, Cole P

Dept. Social and Preventive Medicine, Laval U., Quebec City, Quebec, G1K 7P4, Canada

Am J Epidemiol; 115(3):428-437 1982

The authors conducted a case-control study at two Boston, Massachusetts area hospitals to evaluate the relation of anatomic features of the breast, visible on the xeromammogram, to the risk of breast cancer. The cases were 408 women with newly diagnosed breast cancer and the controls were 1,021 women without signs or symptoms of breast disease. The features of the breast assessed were the 'parenchymal pattern' as defined by Wolfe and specific radiologic characteristics which are components of the parenchymal pattern classification. Women whose mammogram showed the P2 or DY parenchymal patterns were at elevated risk compared to women with the N1 pattern. Further, risk increased regularly with increases in the percentage of the breast that showed nodular densities and with increases in the av size and concentration of these densities. Women with extensive homogeneous density were also at elevated risk. These findings were observed only among women aged 20-59 yr. In this group, women with nodular densities in 60% or more of the breast appeared to have a five-fold increase in risk compared to women without nodular densities in the breast. (Author abstract) (22 Refs)

9. FAMILIAL HEREDITY IN BREAST CANCER.

Frollini F, Terzani L, Barretta M, Arnesano PG, Meussi C

III Divisione di Chirurgia Generale, Ente Ospedaliero Elena d'Aosta, Napoli, Italy

Rass Int Clin Ter; 61(15):1042-1044 1981

Two sisters 1 yr apart had bilateral mammary cancer (MC). One sister had Halsted's mastectomy (MA) of the right breast when she was 54 yr old, followed 2 yr later by the same type of MA on the left breast. Roentgen radiotherapy was administered. Many local skin metastases appeared and were removed surgically. No distant metastases were observed in greater than 5 yr follow-up and the patient was in excellent health otherwise. The second sister had MA first on the right breast, followed by MA on the left breast. Lymph node involvement was observed in two nodes on one side and three on the other. The patient received six cycles of the chemotherapy consisting of cyclophosphamide, methotrexate, and 5-fluorouracil; she did not have local or distant metastases and was in excellent health. The mother of the two sisters, her parents, and another daughter from previous marriage did not have any history of cancer. The father of the two sisters had parotid cancer with liver metastases. His brother died of pulmonary cancer and his daughter died due to cerebral tumor. Familial history of cancer should be considered an important risk factor in MC. (13 Refs) (In ITA)

10. EFFECT OF AGE AT FIRST CHILDBIRTH ON RISK OF DEVELOPING SPECIFIC HISTOLOGIC SUBTYPE OF BREAST CANCER.

LiVolsi VA, Kelsey JL, Fischer DB, Holford TR, Mostow ED, Goldenberg IS

Dept. Pathology, Yale Univ. Sch. Medicine, 310 Cedar St., New Haven, CT, 06510

Cancer; 49(9):1937-1940 1982

Epidemiologic variables related to breast cancer risk were assessed in a case-control study of 332 women with breast carcinoma and 1,353 comparison women. Risk factors for breast cancer as a whole included nulliparity, late age at first childbirth, early age at menarche, late age at menopause, personal history of benign breast disease, family history of breast cancer, and among postmenopausal women, body weight. These risk factors were then analyzed with respect to histologic subtype of breast cancer involved, ie, duct-derived or lobular tumors, to determine whether the association between any of the risk factors and breast cancer varied according to histopathologic subtype. Histologic subtype for the 316 cases reviewed included 284 duct cancers and 32 lobular carcinomas. Although slight differences were noted among some of the risk factors and the variety of cancer, none of the differences was marked except for the variable age at first birth. For ductal carcinoma, the risk was highest among nulliparous women and decreased the younger a woman was at the time she gave birth to her first child. The risk of infiltrating lobular carcinoma, however, was lowest among nulliparous females or those who had given birth at a young age and increased the older a woman was when she gave birth to her first child. (Author abstract) (9 Refs)

11. ASSOCIATION OF FUNCTIONAL OVARY NEOPLASIA, ENDOMETRIAL ADENOCARCINOMA, AND CYSTIC BREAST DISEASE.

Morgera P, Tolotti M

Centro per la prevenzione e la cura dei tumori della sfera genitale, femminile Ente Ospedaliero Regionale Specializzato - Ospedali dei Pellegrini, Napoli, Italy

Rass Int Clin Ter; 61(15):1023-1033 1981

A 74-yr-old woman with two children stopped menstruating when she was 50 yr old; when she was 66 yr old due to hematic vaginal discharge a curettage was performed. With histologic diagnosis (HD) of cystic glandular hyperplasia of endometrium and the same symptoms, curettage was repeated twice (3, and 5 yr) after the first episode. The patient had hematic vaginal discharge, enlarged uterus, and ovarian tumor. After surgery, HD was granulosa cell carcinoma of the ovary and poorly differentiated adenocarcinoma of endometrium with uterine fibrosis. According to International Federation of Gynecology and Obstetrics (FIGO) classification the uterine carcinoma was IAg2 and the ovarian carcinoma was IA (2) gl. The patient was administered telecobalt therapy. Four mo later the patient had tumor and pain in the left breast. Surgery was performed and the histologic examination indicated cystic disease of mammary gland with light degree of intraductal epitheliosis. One cyst showed active inflammation of the wall. The patient was well at follow-up 6 mo and 1 yr later. (59 Refs) (In ITA)

12. THE RELATION OF MAMMOGRAPHIC FEATURES OF THE BREAST TO BREAST CANCER RISK FACTORS.

Brisson J, Sadowsky NL, Twaddle JA, Morrison AS, Cole P, Merletti F

Dept. Social and Preventive Medicine, Laval U., Quebec City, Quebec, G1K 7P4, Canada

Am J Epidemiol; 115(3):438-443 1982

The authors evaluated the relation of breast cancer risk factors to the appearance of the breast on xeromammograms. Subjects were 1,021 women without breast cancer whose first xeromammographic examination at one of two Boston, Massachusetts area hospitals was done for a reason described as 'baseline' or 'routine'. The principal mammographic features assessed were the percentage of the breast showing nodular densities and the percentage showing homogeneous density. The extent of nodular and homogeneous densities decreased as age increased. The amount of both types of density decreased with increase in the number of full-term pregnancies. The percentages of the breast showing nodular and homogeneous densities were slightly higher for premenopausal compared to postmenopausal women, and for women with a history of breast biopsy or aspiration compared to women without. Certain characteristics of observed relations between risk factors and mammographic features differed for the two types of densities. (Author abstract) (14 Refs)

13. GENITAL CANCER AND PRECANCEROUS LESIONS IN WOMEN WITH KIDNEY TRANSPLANTS. A STUDY OF 90 CASES.

Pelissier C, Yaneva M, Joubert E, Peretz M, Rochet Y

Service d'Endocrinologie de la Reproduction, Hopital Necker, 149, rue de Sevres, F 75730 Paris, France

Gynecologie; 32(4/5):359-365 1981

A study of benign and malignant genital lesions in 90 women who had undergone renal transplants 3 mo-17 yr previously is reported. Av age at the time of consult for kidney disease was

32.8 yr. Immunosuppressive therapy was given to 89/90 women. One patient who underwent two transplants received total irradiation and thymic irradiation. Two patients were treated for cervical cancer during the time of their dialysis. At follow-up, several cancerous, precancerous, and benign lesions were found. These include one invasive cancer of the uterus, one case of in situ vaginal cancer with degeneration of a viral papilloma, one case of breast cancer, two cases of cervical dysplasia, four cases of moderate dysplasia associated with cervical viral papillomatosis, three viral papillomas, three primary herpetic cervical infections, one case of Bowenoid dysplasia and one case of sclero-atrophic lichen without malignant changes, in the vulva. The papillomatous lesions had not been mentioned in the other seven studies on genital cancer in women with kidney transplants. It is suggested that further studies may elucidate of immunosuppressors in the development of cancerous and papillomatous lesions. (26 Refs) (In FRE)

14. ATYPICAL DISCHARGE FROM THE BREAST DURING PREGNANCY AND/OR LACTATION.

O'Callaghan MA
Nursing Mothers' Assoc. Australia, Hawthorn, Australia
Aust NZ J Obstet Gynaecol; 21(4):214-216 1981

A blood-like discharge from the breasts only during the pregnancy or before establishment of lactation should be considered unusually but not abnormal, and it is not a contraindication for breast feeding. A review of 37 cases involving 32 women indicates that this discharge is seen in the 1st pregnancy usually bilaterally, and as early as the 4th mo. Hypotheses on the pathology are presented, including benign tumor and intraductal papilloma. (13 Refs)

15. BREAST CANCER IN ARABIC WOMEN.

Hoogstraten B, Gad-el-Mawla N, Hamsa MR, Abdelaziz I, Omar Y
Cancer Treatment Center, Bethesda Hosp., 619 Oak St., Cincinnati, OH, 45206
Oncology; 39(3):134-139 1982

A case-control study of breast cancer was conducted in Cairo, Egypt and in Kuwait. This is the first such report from Arabic countries and the most significant finding is the annual incidence rate of 7.67 per 100,000 in Kuwaiti women, which ranks amongst the lowest thus far reported in the world. Factors which contribute to this low rate are a short period of active menstruation, low family history, first childbirth at very early age and most likely significant dietary factors. More than 45% of Egyptian women give birth to a child before the age of 20, with 56.5% of controls and 42.3% of patients (p less than 0.01). Many patients already have extensive disease at time of diagnosis as a result of considerable delay. However, this delay did not result in a high incidence of inflammatory breast carcinoma, such as has been reported in Tunisia. (Author abstract) (21 Refs)

16. BREAST CANCER AND THE CONDOM.

Tibblin G
Memorial Univ. Newfoundland, St. John's, Newfoundland, Canada
Clin Invest Med; 4(3/4):153-154 1981

The relationship between barrier contraception, human semen, and the incidence of breast cancer is discussed. In one retrospective study of 153 breast cancer patients and 168 age-matched controls, 71.9% of the breast cancer patients used barrier contraceptive methods or had husbands with characteristics of male infertility, whereas only 35.7% of the control group used barrier methods or had husbands with low fertility. Implications of the findings are discussed. (2 Refs)

17. THE PROBLEM OF MULTIPLE BREAST CANCERS.

Kegel W, Schmieder A
Klinik fur Strahlendiagnostik, Kliniken der Landeshauptstadt, Saarbrucken-Winterberg Akademisches Lehrkrankenhaus, D-6600 Saarbrucken, W. Germany
Roentgenblaetter; 35(2):62-65 1982

In a retrospective study multiple breast tumors were found in 26/368 women undergoing radiotherapy for breast cancer (BC). Bilateral occurrence was simultaneous in 12 cases and successive in 14 cases. The possibility of metastasis as the cause of the multiple cancers was excluded in all 26 cases. Av age of women with simultaneous bilateral cancers was 65.2 yr; av age of women with successive cancers was 48.7 yr at diagnosis of the first cancer. The interval between first and second cancers was 1-36 yr (av 11.2 yr). Distant metastases were not found in any cases. Second tumor was detected by mammography in most cases of simultaneous tumors; only one successive tumor was detected by mammography. Occurrence of multiple BC reflected a cancerogenic process with multicentric, bilateral effects, rather than a locoregional disease. Diagnosis and therapy should, therefore, take into account such factors as genetic tendencies, environmental influences, and hormonal predispositions. Patients undergoing unilateral mastectomy should be carefully monitored for subsequent BC in the remaining breast. (26 Refs) (In GER)

POSSIBLE IATROGENIC FACTORS IN HUMAN BREAST CARCINOGENESIS

18. SIDE-EFFECTS OF AZATHIOPRINE TREATMENT IN RHEUMATOID ARTHRITIS: ANALYSIS OF 10 YEARS OF EXPERIENCE.

Speerstra F, Boerbooms AM, Van de Putte LB, Van Beusekom HJ, Kruijsen MW, Vandenbroucke JP
Dept. Rheumatology, St. Radboud Hosp., Nijmegen, The Netherlands
Ann Rheum Dis; 41(Suppl1):37-39 1982

Azathioprine (APR: 1.5-2 mg/kg/day) was given to 25 men and 66 women (median age 54 yr) with active rheumatoid arthritis (RA) of 1-33 yr duration (median, 9 yr). At the beginning of APR therapy, 53 patients were receiving corticosteroids. Previous treatment had included cyclophosphamide or chlorambucil in 5/91. APR was discontinued in 29 patients for a variety of reasons, but only 7/29 had failed to respond. Most patients showed prolonged remissions during continuous APR treatment. The median duration of APR treatment was 36 mo (median total dose, 120 g). Some patients tolerated APR for greater than 10 yr. The median follow-up period was 5 yr. During follow-up, 7/25 men and 5/66 women died. The commonest causes of death were malignancies (6/12: 4 bronchus, 1 kidney, 1 breast) and myocardial infarction (3/12). The standardized mortality ratios (SMR) for all causes combined were 3.7:1 in men (102 patient-yr) and 1.6:1 in women (292 patient-yr of observation). The SMRs for malignancies were 6.7:1 in men and 2.1:1 in women. All deaths in APR-treated men were caused by bronchial cancer (4/7 deaths) or myocardial infarction (3/7); they may have been related to cigarette smoking (96% of the group). The APR-treated patients who developed cancer did not differ from the patients who did not develop cancer with regard to the total APR dose or the duration of treatment. At the time of report, 79 patients were alive and being followed up regularly, and none had any signs of lymphoproliferative or other malignancies. (30 Refs)

19. LONG-TERM EFFECTS OF AZATHIOPRINE IN RHEUMATOID ARTHRITIS.

Urowitz MB, Smythe HA, Able T, Norman CS, Travis C
Rheumatic Disease Unit, Wellesley Hosp., 160 Wellesley St. E., Toronto, Ontario, M4Y 1J3, Canada
Ann Rheum Dis; 41(Suppl1):18-22 1982

Potential early signs of malignancy were assessed in 36 patients (8 men, 28 women; mean age 57.8 yr) receiving azathioprine (APR: mean, 1.08 mg/kg/day x 38.5 mo) for rheumatoid arthritis and 49 controls (13 men, 36 women; mean age 51.4 yr) not receiving APR. The mean duration of arthritis was somewhat longer in the APR group (15.3 vs 11.9 yr). The groups were comparable in their symptomatic status, chest x-rays, and most laboratory test results. As compared to the controls, the APR groups showed significantly lower WBC counts, a higher frequency of megaloblastic features in the bone marrow, lower serum folate levels, and a higher frequency of chromosomal aberrations in the bone marrow. Malignancies had occurred in first-degree relatives of 15/36 APR-treated patients and 6/49 controls. The APR and control groups showed comparable frequencies of inflammatory or fibrotic pulmonary abnormalities (15/36 vs 9/49), benign breast masses (1/28 vs 3/36 women), and abnormal urine cytology (4/36 vs 1/49) with no evidence of cancer on follow-up. Neoplasms were observed in 7/36 APR patients (3/7 were malignant or potentially malignant tumors) and 5/49 controls (1/5 was a malignant tumor); the difference in incidence rates were not significant. The only non-Hodgkin's lymphoma observed in the group was in a control patient. In the APR group, the tumors developed after a mean of 1.6 yr of APR therapy. Three APR-treated patients with cancer had positive family histories of cancer; none of the controls with tumors had family histories of cancer. Elevated titers of alpha-fetoprotein or carcinoembryonic antigen were observed in some of the APR group (1/36 and 7/25 patients tested, respectively; none of these patients had a detectable cancer) and none of the controls. Further studies in larger groups of APR-treated patients and longer treatment periods are recommended. (53 Refs)

20. THE COMPARATIVE INCIDENCE OF MALIGNANT DISEASE IN RHEUMATOID ARTHRITICS EXPOSED TO DIFFERENT TREATMENT REGIMENS.

Hazleman BL, De Silva M
Dept. Rheumatology, Addenbrooke's Hosp., Hills Road, Cambridge, England
Ann Rheum Dis; 41(Suppl1):12-17 1982

Follow-up data for a 11-yr period were obtained for 311 patients with classic rheumatoid arthritis (RA), including 214 patients treated with azathioprine (APR), 52 patients given APR in combination with either cyclophosphamide (CP) or chlorambucil (CB), 11 patients given CP or CB without APR, and 97 patients given no cytotoxic agents. The durations of cytotoxic therapy were 0.2-8 yr for CP or CB and 1-11 yr (mean, 2.5 yr) for APR. During the 11 yr follow-up period, 46 patients died (19 of cardiovascular diseases, 13 of cancer) and 20 patients developed cancer, mostly of the lung or bronchus (5), breast (4), or prostate (2). Neoplasms developed in 10/214 patients receiving cytotoxic therapy (5%) and 10/97 patients receiving no cytotoxic therapy (10%). Although RA itself was associated with a high frequency of neoplasms, neoplasms were not associated with immunosuppressive treatment. The duration of cytotoxic therapy in the cancer patients (0.3-8 yr) resembled the duration of treatment in the patients who did not develop cancer. The RA group as a whole showed higher death rates for all causes combined in the 45-64 age group (with a nonsignificant increase in deaths from ischemic heart disease and cancer) and a lower-than-expected death rate in the 75+ age group. The only non-Hodgkin's lymphoma observed in the RA group was in a patient who received no cytotoxic therapy. One patient developed multiple recurring bladder neoplasms (controlled by repeated surgery) after 8 yr of CP therapy. CP should be given with caution to patients with nonmalignant diseases. Intermittent courses of CP should be given if possible, and prolonged CP therapy should be avoided. (41 Refs)

21. BREAST CANCER AND THE PILL. NO CLEAR EVIDENCE OF AN ASSOCIATION HAS YET BEEN DEMONSTRATED.

Fraser IS
No affiliation given
Med J Aust; 1(1):6 1982

Despite suggestions of a relationship between use of oral contraceptives and breast cancer, two recent cohort studies and a matched control study have shown no consistent significant increase or decrease in the risk of breast cancer between any group of oral contraceptive users and their controls. The possible risk for young women using the Pill for many yr before their first pregnancy is considered. Problems associated with studying the long-term risks of the Pill are discussed. (10 Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

22. SPONTANEOUS TUMORS IN CONTROL F344 AND CHARLES RIVER-CD RATS AND CHARLES RIVER CD-1 AND B6C3HF1 MICE.

Sher SP, Jensen RD, Bokelman DL
Dept. Safety Assessment, Merck Sharp and Dohme Res. Lab., West Point, PA, 19486
Toxicol Lett; 11(1/2):103-110 1982

Spontaneous tumor incidence in an inbred rat strain (F344), an outbred rat strain (Charles River-CD: CR-CD), an F1 hybrid mouse (B6C3HF1), and an outbred strain of mouse (Charles River-CD-1: CR-CD-1) were compared. Carcinogenic studies performed by Lab A and Lab B were scanned to determine control F344 rat and B6C3HF1 mouse tumor incidence. Carcinogenic studies performed by Merck Sharp and Dohme Laboratories (MSDL) were scanned to determine control CR-CD rat and CR-CD-1 mouse tumor incidence. B6C3HF1 mouse tumor incidence varied from 10-89% in Lab A and 13-80% in Lab B. Tumor incidence in CR-CD-1 mice was 38-40%; frequent tumor sites included the lung and lymphoreticular system. F344 rat tumor incidence varied from 96% in males to 62 or 78% in females; common tumors in males were benign testicular interstitial cell tumors, and in females, pituitary and mammary tumors. Tumor incidence in CR-CD rats was 71-88%; frequent tumor sites included the testes and the pituitary gland in males, and the pituitary and mammary glands in females. Considerable variation in tumor incidence was observed in individual studies regardless of the strain and there was often greater variation in incidence between laboratories using the same strain than between different laboratories using unlike strains. Sufficient historical tumor data must be developed on the strain used in a particular test laboratory. (10 Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

23. EFFECTS OF HYPOTHYROIDISM ON DEVELOPMENT OF NITROSOMETHYLUREA-INDUCED TUMORS OF THE MAMMARY GLAND, THYROID GLAND, AND OTHER TISSUES.

Milmore JE, Chandrasekaran V, Weisburger JH

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Proc Soc Exp Biol Med; 169(4):487-493 1982

Female Fischer 344 rats were injected iv with 50 mg/kg N-nitrosomethylurea (NMU) at 50 days of age; some also received 0.3, 1.0, or 3.0 mg propylthiouracil (PTU) per 100 ml of drinking water, beginning 5 days after the NMU administration, and others received 131I injections. Six wk after treatment, serum thyroxine levels were elevated in rats receiving NMU only, but not in those receiving PTU as well, whereas a 10 uCi dose of 131I caused a slight but significant depression of serum thyroxine level. PTU or 131I increased the incidence of benign and 1 malignant mammary tumors, except in rats receiving the highest PTU dose, which had a decreased incidence of malignancies. Weights of ovaries, uteri, or adrenal glands were unaffected by NMU or PTU. Malignant neoplasms were adenocarcinomas that were sometimes multiple. Benign thyroid tumors were follicular adenomas; malignant thyroid tumors were mostly follicular, or follicular mixed with papillary carcinoma. Numerous other neoplasms appeared in other systems. Slight hypothyroidism could increase the incidence of NMU-induced mammary tumors in the rat, but when hypothyroidism was severe enough to limit growth, tumor incidence was less. (32 Refs)

24. INFLUENCE OF ESTRADIOL ON THE TOTAL UPTAKE AND INCORPORATION OF THYMIDINE IN HUMAN BREAST CANCER (MCF-7) IN LONG-TERM CELL CULTURE: COMPARISON OF AUTORADIOGRAPHIC AND BIOCHEMICAL METHODS.

Coosen R, De Jong PW, Schwarz F

Dept. Endocrinology, Univ. Hosp., 3511 GV Utrecht, The Netherlands

Mol Cell Biochem; 42(3):155-160 1982

The total uptake and incorporation into DNA of 3H-thymidine in MCF-7 cells is stimulated by estradiol after an incubation period of 24 hr. Prolonged incubations show a decreased rate of both uptake and incorporation of 3H-thymidine, but the labeling index remains elevated up to 48 hr. It appears that this is the only exception to the observed good relationship between labeling index and total uptake of 3H-thymidine. This correlation may be of use in comparing autoradiographic and biochemical data on DNA synthesis in the case of culturing both primary mammary tumors and mammary cancer cell lines. (Author abstract) (22 Refs)

25. PREGNANCY STIMULATES DNA SYNTHESIS IN R3230AC MAMMARY ADENOCARCINOMA.

Orloski JM, Fritz PJ, Liu DK
(c/o Liu) Dept. Pharmacology, Specialized Cancer Res. Center, Milton S. Hershey Medical Center, Pennsylvania State Univ. Coll. Medicine, Hershey, PA, 17033
Eur J Cancer Clin Oncol; 18(1):99-106 1982

The transplantable R3230AC mammary adenocarcinoma was grown in virgin, pregnant and lactating rats and in vivo rates of [3H]-thymidine incorporation into DNA and acid-soluble dTTP were compared between tumor and host mammary glands. The tumor differed from the host gland in that the rates of uptake and phosphorylation of the injected thymidine remained unchanged throughout the lactation cycle, but the dTTP pool increased greatly during pregnancy throughout the lactation cycle, but the dTTP pool increased greatly during pregnancy and declined during lactation. In both tumor and host glands, DNA labeling rates were higher during pregnancy than during lactation. Tumor DNA synthesis rates, in terms of incorporated dTMP, increased markedly during pregnancy and returned to pre-pregnant rates following parturition and during lactation. This pattern was similar to host mammary glands, but the change was of a greater magnitude. The data illustrate the usefulness of growing a transplantable mammary tumor in rats of varying physiological states. This way, similarities and differences between a mammary tumor and the host mammary gland regarding their responses to the hormonal milieu of pregnancy and lactation can be assessed. (Author abstract) (48 Refs)

26. HORMONAL REGULATION OF NET DNA SYNTHESIS IN MCF-7 HUMAN BREAST CANCER CELLS IN TISSUE CULTURE.

Aitken SC, Lippman ME
(c/o Lippman), NCI, NIH, Building 10, Room 6B02, Bethesda, MD, 20205
Cancer Res; 42(5):1727-1735 1982

Estrogens and anti-estrogens have striking effects on growth of target tissues in vivo. In order to examine these effects in vitro, experimental methods for the rigorous assessment of rates of net DNA synthesis in tissue culture systems are required. The quantitation of DNA synthesis with inorganic [32P]orthophosphate is described. The limitations of more conventional [3H]thymidine labeling are illustrated in this hormonally responsive system. Estrogen administration increases the specific activity of acid-soluble phosphate and increases net DNA synthesis relative to controls in MCF-7 human breast cancer cells. Stimulation is most evident after 36 hr of hormone treatment. Conversely, tamoxifen produces substantial inhibition of net DNA synthesis after 36 hr of hormone treatment. Thymidine availability modulates the effect of estrogens and anti-estrogens on DNA synthesis and constitutes an independent experimental variable. (Author abstract) (55 Refs)

27. RAT MAMMARY TUMORS FROM CARCINOGEN-INDUCED NODULES AND THEIR RESPONSIVENESS TO OVARIECTOMY.

Rivera EM, Vijayaraghavan S
Dept. Zoology, Michigan State Univ., East Lansing, MI, 48824
Eur J Cancer Clin Oncol; 18(1):53-58 1982

The research objective was to determine whether DMBA-induced rat mammary tumors derived from transplanted mammary nodules differ in ovarian-responsiveness from tumors originating randomly from in situ mammary parenchyma. Nodule-derived tumors were from hyperplastic alveolar outgrowths in mammary fat pads, which were either first generation outgrowths (primary nodule outgrowths) or generations 3-6 of a tumorigenic nodule line (nodule outgrowth line T18). Tumors were induced in primary outgrowths by secondry exposure to DMBA in vivo or in vitro. The nodule line was not re-exposed to DMBA because of its high oncogenicity (80-85%). Despite the histological similarity of the tumor derivatives, primary nodule outgrowths and the nodule outgrowth line developed a higher proportion of ovarian-independent to ovarian-dependent tumors (1:3 and 3:4 respectively) than did in situ mammary tissues (1:9). These results are consistent with the observation that nodule outgrowths were themselves ovarian-independent. (Author abstract) (13 Refs)

28. PROLACTIN STIMULATION OF ORNITHINE DECARBOXYLASE ACTIVITY IN CULTURED RAT MAMMARY TUMORS.

Frazier RP, Costlow ME

Dept. Biochemistry, St. Jude Children's Res. Hosp., Memphis, TN, 38101

Exp Cell Res; 138(1):39-45 1982

Ovine prolactin increased ornithine decarboxylase (ODC) activity in 13 of 14 primary cultures of 7,12-dimethylbenzanthracene-induced rat mammary tumors. The 27-436% increase (mean 219%) in ODC activity required a 3-hr incubation with at least 1,000 ng prolactin/ml. Lower prolactin concentrations were ineffective. Bovine fetal serum or other hormones were not required for the prolactin effect. Addition of dibuturyl cyclic AMP (db-cAMP) (2.5 mM) to cultures increased ODC activity two-fold, whereas dibuturyl cyclic GMP (db-cGMP) (2.5 mM) had little effect. When either nucleotide plus 10 or 100 ng prolactin/ml was added. ODC activity increased three- to four-fold. These results show that increased ODC activity is an early event in prolactin action in cultured rat mammary tumor cells. The cyclic nucleotides appear to be necessary for the cells to respond to physiologic levels of hormone. (Author abstract) (33 Refs)

29. EFFECT OF THE HORMONAL STATUS DURING THE PRETUMORAL PERIOD ON THE BIOLOGICAL PROPERTIES OF MAMMARY GLAND TUMORS IN C3H/HE MICE.

Vasnetsova SS, Gutnik NS, Turkevich NM

R. E. Kavetskii Inst. Problems of Oncology, Kiev, USSR

Eksp Onkol; 4(1):70-72 1982

The effect of the hormonal status during the preneoplastic period on the incidence and properties of mammary gland neoplasms was studied in 1.5-mo-old C3H/He mice. Group I consisted of virgin females, Group II consisted of females with normal reproductive cycle, and Group III consisted of mice subjected to enhanced reproduction (frequent pregnancies without lactation). The incidence of mammary gland tumors in Groups I, II, and III was 61%, 74%, and 82%, respectively. The av latent period of tumor development was 300, 294, and 247 days, respectively. The tumors in Group III were less differentiate than those in Groups II and I. (15 Refs) (In RUS)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

30. TUMOR IMMUNITY IN THE MAMMARY GLAND.

Miller FR, Heppner GH

Dept. Immunology, Michigan Cancer Foundation, 110 East Warren Ave., Detroit, MI, 48201

Cancer Immunol Immunother; 12(2):173-176 1982

The principle of immune privileged sites was examined with regard to the growth in mice of mouse mammary tumor 410, which was derived from a spontaneously growing BALB/cf C3H mammary tumor, following injection into mammary fatpad and sc injection. No evidence of immune privileged sites was found for tumor 410 in seven experiments. The ability to express immunity, the efferent arm of the immune response, to tumor 410 was functional in the fatpad. Temporary growth of the tumor in the mammary fatpad rendered the mice resistant to tumor challenge in the contralateral fatpad. The ability to induce immunity, the afferent arm, was as well developed in the fatpad as in the subcutis. The specificity of the immune response in the fatpad was demonstrated. Animals specifically immunized to a syngeneic rhabdomyosarcoma were specifically resistant to the rhabdomyosarcoma, while growth of tumor 410 was unaffected. (18 Refs)

31. MACROPHAGES IN HUMAN TUMOURS: AN IMMUNOHISTOCHEMICAL STUDY.

Nash JR

Nuffield Dept. Pathology, Univ. Oxford, John Radcliffe Hosp., Oxford, England

J Pathol; 136(2):73-83 1982

Human gastrointestinal, breast, and other tumors were stained for acid phosphatase (AP), non-specific esterase (NSE), and lysozyme to assess the usefulness and specificity of the methods in assessing tumor macrophage content. Of the 48 tumors studied by lysozyme staining, 22 were studied with NSE staining and 9/22 were further studied by AP staining. All colonic tumors contained few lysozyme-positive macrophages (LPM) within the tumor, an amount similar to the surrounding non-malignant mucosa. Most colonic tumors showed LPM concentrated around the tumor edge; this was less apparent in tumors from more proximal parts of the gastrointestinal tract. Negligible macrophage infiltration was found in 13//15 breast carcinomas. Other tumors showed negligible numbers of macrophages, with the exception of a metastatic squamous carcinoma deposit in a lymph node and a transitional cell carcinoma of the bladder. Normal and inflamed tissues contained variable numbers of macrophages, and lysozyme staining was often very faint in epithelioid and giant cells. AP and NSE staining was more difficult to assess because there often was no way to discriminate between tumor cells and macrophages, both of which were stained. Both of the stains, particularly NSE, detected more cells than lysozyme. With NSE, epithelia were often densely stained, and tumors with single cell infiltration were often impossible to assess for macrophage content. AP stained tumor and epithelial cells less strongly than NSE but often produced a fine granular positivity within them. (18 Refs)

32. MONOCLONAL ANTIBODIES AGAINST HUMAN MILKFAT GLOBULE MEMBRANES DETECTING DIFFERENTIATION ANTIGENS OF THE MAMMARY GLAND.

Hilkens J, Buijs F, Hilgers J, Hageman P, Sonnenberg A, Koldovsky U, Karande K, Van Hoeven RP, Feltkamp C, Van de Rijn JM
Div. Genetics and Experimental Animals, Netherlands Cancer Inst., Amsterdam, The Netherlands
Protides Biol Fluid Proc Colloq; 29:813-816 1982

Monoclonal antibodies of mouse origin were raised against antigens of highly purified human milkfat globule membranes. Immunoprecipitation followed by sodium dodecyl sulfate gel electrophoresis revealed five groups of antigens which varied as regards association with milk proteins and in tissue distribution in normal and malignant mammary glands. (15 Refs)

33. APPLICATION OF HUMAN EMBRYONIC ANTIGEN FOR IDENTIFICATION OF IMMUNE RESPONSE IN CANCER PATIENTS.

Gorodilova VV, Mandrik EV, Ul'chenko VM
P. A. Herzen Res. Inst. Oncology, RSFSR Ministry Health, Moscow, USSR
Vopr Onkol; 28(1):23-27 1982

The study was concerned with a comparison of immune response to antigen obtained from human embryonic intestine in patients with malignant and benign tumors of the breast and ovaries, cancer of the urinary bladder, cases of various inflammatory diseases and healthy controls. Application of this marker in the skin test of time-delayed hypersensitivity reaction provided a means of evaluation of tumor-associated immunological vigor. The results point to the similarity of skin reactions of time-delayed hypersensitivity in cases of mastopathy and early stages of breast cancer. Therefore, human embryonic antigen may be used as an additional criterion of assessment of immunocompetence of patients with precancerous lesions and malignant neoplasms. (Author abstract) (10 Refs) (In RUS)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

34. A VIRUS-RELATED PROTEIN IN HUMAN BREAST CANCER.

Spiegelman S, Mesa-Tejada R, Ohno T, Ramanarayanan M, Nayak R, Baush J, Fenoglio C, Keydar I
Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY
Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Examination of validity of the viral transformation mechanism is described. Topics discussed include testing the diagnostic utility of particle proteins with the murine mammary model, immunohistological localization of murine mammary tumor virus in mouse mammary tumors, immunological detection in human breast carcinomas (BC), malignant breast tissues, normal and benign breast tissues, apocrine metaplasia, malignancies other than BC, specificity of the immunoperoxidase reaction in human BC, and the role of sugar residues in the crossreactivity of 52,000 dalton glycoprotein with the human breast cancer antigen. Experiments showed that particles detected possess the key diagnostic features as well as the density and size of oncornaviruses. (37 Refs)

35. ESTABLISHMENT AND CHARACTERIZATION OF SV40-TRANSFORMED HUMAN BREAST EPITHELIAL CELL LINES.

Chang SE, Keen J, Lane EB, Taylor-Papadimitriou J
Imperial Cancer Res. Fund, P.O. Box 123, Lincoln's Inn Fields, London WC2A 3PX, England
Cancer Res; 42(5):2040-2053 1982

Human breast epithelial cells cultured from milk have been transformed with SV40. Indirect immunofluorescence tests using monoclonal antibodies show that cells from clones grown in soft agar have SV40 large T-antigen in their nuclei and epithelia-specific tonofilament antigens on their intermediate filaments. In primary cultures of milk epithelial cells, the tonofilaments form a characteristic delicate basketwork throughout the cytoplasm, but in the SV40-transformed epithelial cell strains, the filament network is grossly distorted. Insulin, hydrocortisone, and serum stimulate the growth of the cell strains. At passages 8 to 11, the cell strains become quiescent and usually die. One cell strain survived this crisis period and gave rise to the fR series of cell lines. Most cell lines have a cuboidal morphology and react with a monoclonal antibody that recognizes a differentiation antigen on the membranes of breast epithelia. Line fR2 expressed the highest level of this antigen whereas fR5, the only fR line isolated with fusiform morphology, had relatively little. The in vitro-transformed lines may be related to the two dominant epithelial cell types seen in primary milk cultures and could be useful for studying the relationship between transformation and differentiation in human mammary epithelial cells. (Author abstract) (36 Refs)

36. RADIOIMMUNOLOCALIZATION OF MURINE MAMMARY TUMOR VIRUS PROTEINS IN GELS.

Bausch JN, Prasad KS, Spiegelman S
(c/o Spiegelman) Inst. Cancer Res., Coll. Physicians and Surgeons, Columbia Univ., New York, NY, 10032
Anal Biochem; 119(2):293-298 1982

A procedure for the immunological detection of antigens on sodium dodecyl sulfate-polyacrylamide gels using iodinated antibodies combined with an immunoconcentration step to enrich for the desired antigen(s) is described. This selective enrichment is achieved by separation of the antigen-antibody complexes with formalin-treated cells of Staphylococcus aureus and is followed by radioimmunolocalization on gels. This method is particularly useful for the characterization of antigens present at low concentrations in complex biological fluids. Its usefulness is exemplified here by the successful identification of mouse mammary tumor virus antigens in extracts of murine mammary tumors and in plasmas of tumor-bearing animals. In particular, the procedure permits the ready determination that the gp52 protein detected in the plasmas of tumor-bearing animals is in fact present as a 52,000-dalton species and not as a higher mol wt precursor. (Author abstract) (17 Refs)

37. MOUSE MAMMARY TUMOR VIRUS DNA SEQUENCES IN TUMORIGENIC AND NONTUMORIGENIC CELLS FROM A MAMMARY ADENOCARCINOMA.

Morris VL, Gray DA, Jones RF, Chan EC, McGrath CM
Dept. Microbiology and Immunology, Univ. Western Ontario, London, Ontario N6A 5C1, Canada
Virology; 118(1):117-127 1982

If BALB/c mice are foster nursed on C3H mice, which contain milk-borne mouse mammary tumor virus (MMTV) associated with a high mammary tumor incidence, their tumor incidence rises from less than 1 to 89.5% by 12 mo; in addition, there is an increase in the integrated MMTV DNA sequences in these mammary tumors. To investigate if all or only a few of these added MMTV DNA sequences are associated with tumorigenicity, we separated tumorigenic and nontumorigenic epithelial cells from a single mammary adenocarcinoma using primary methocel cultures. The MMTV DNA sequences from these cultures were then examined using restriction endonuclease analysis. Our results indicated that the methocel colonies isolated from a single mammary adenocarcinoma were heterogeneous with respect to their integrated MMTV DNA sequences. We also found that not all newly acquired MMTV DNA copies were associated with tumorigenicity. In addition, in one tumorigenic subline we detected only a single integrated copy. Our data thus suggest that the site of integration is more important than the total number of integrated MMTV DNA sequences. Furthermore, tumorigenicity did not seem to be linked to continued transcription of high levels of a major portion of the MMTV genome. (Author abstract) (28 Refs)

38. HORMONE-DEPENDENT MATURATION OF MAJOR STRUCTURAL PROTEINS OF MURINE MAMMARY CANCER VIRUS.

Beriashvili MM, Chernova OB, Kolobkov SL, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Vopr Virusol; (1):34-38 1982

The effects of hormones on the processing of major structural proteins of murine mammary cancer virus (MMCV) were studied in virus-producing cells of mammary gland carcinoma of IK mice. Expression of the virus-specific products was assayed by radioimmunoprecipitation technique. Celles cultured in the hormone-free medium showed an expression of the products of gag and env genes. Incubation of cells with insulin and with dexamethasone resulted in marked stimulation of the processing of major glycoprotein of the virion envelope (gPr 70env). (10 Refs) (In RUS)

RADIOLOGICAL ASPECTS OF MAMMARY GLAND CARCINOGENESIS

39. EFFECTS OF LOW-DOSE RADIATION. A CORRELATION STUDY.

Ediing C, Comba P, Axelson O, Flodin U
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Scand J Work Environ Health; 8(Suppl1):59-64 1982

Based on information in the literature, five types of malignancies (lung, breast, and pancreatic cancer, leukemia, and multiple myeloma) as probably respondent to irradiation induction and therefore likely to correlate with background radiation were chosen for the correlation study on effects of low-dose radiation. Mortality rates age-standardized directly for lung and breast cancer and leukemia during 1969-1978 and for pancreatic cancer and multiple myeloma during 1961-1973 in the counties of Sweden and for persons 40 yr old and over, along with estimates of background radiation (cosmic radiation excluded), Pearson coefficients and p-values are presented. Significant correlation was observed between the estimates of background radiation and lung cancer, for both males and females. A similar correlation was observed for pancreatic cancer in both sexes. Leukemia showed a correlation of borderline significance for males and a weaker correlation for females. Breast cancer (in women only) and multiple myeloma did not show any significant correlation. Risk estimates for lung cancer per working level mo (WLM) and per 10(6) person-yr for persons greater than 50 yr old in various Swedish populations (including Zn-Pb miners) and estimates given in a previous report indicate that 25-35 cases per 10(6) person-yr and per WLM might result from radon daughter exposure. (31 Refs)

40. EVOLVING PERSPECTIVES ON THE EPIDEMIOLOGY AND BIOLOGY OF CANCER: NEEDS AND OPPORTUNITIES.

Upton AC
Inst. Environmental Medicine, New York Univ. Medical Center, New York, NY
Cancer Research in the People's Republic of China and the United States of America: Epidemiology, Causation and New Approaches to Therapy, Proceedings of a Conference held in New York, 28-29, March, 1980. Marks PA, ed. New York, Grune and Stratton, 273 pp., 1981.

Differences in the incidence of cancer (CA) in different parts of the world are presented and the needs and opportunities of research in the epidemiology and biology of CA are discussed. Assumed parameters of a model for estimating CA risks associated with low-level ionizing radiation, estimated risks of radiation-induced CA, and estimates of the annual contribution of radiation exposure to the lifetime burden of fatal CA to the United States (US) population are presented. Time-trends in lung CA mortality and cigarette consumption in England and Wales; incidence of lung CA in regular cigarette smokers in relation to the number of cigarettes smoked/day; time-trends in CA death rates in US males standardized for age; and dose-incidence curves for breast CA in relation to radiation exposure in women surviving atomic-bomb radiation, women treated with x-rays for acute postpartum mastitis, and women subjected to multiple fluoroscopic examinations for pulmonary tuberculosis are presented. (15 Refs)

41. STATISTICAL LIMITATIONS IN RELATION TO SAMPLE SIZE.

Land CE
Environmental Epidemiology Branch, NCI, Bethesda, MD, 20205
Environ Health Perspect; 42:15-21 1981

Examples from radiation carcinogenesis are used to illustrate difficulties in estimating cancer risks for low doses of a carcinogen. Using direct estimation based on data from a population exposed to low doses, an example is given for a linear dose-response relationship for female breast cancer induced by exposure to sparsely ionizing radiation. Leukemia incidence data from a life span study of Nagasaki A-bomb survivors is used to illustrate curve fitting, by which higher dose data determine lower risk estimates. Although more is known about dose-response relationships for ionizing radiation than for any other environmental carcinogen, estimates of cancer risk for low radiation doses have sometimes disagreed by factors of 100 or more. (11 Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

42. THE METABOLISM AND ACTIVATION OF POLYCYCLIC AROMATIC HYDROCARBONS IN EPITHELIAL CELL AGGREGATES AND FIBROBLASTS PREPARED FROM RAT MAMMARY TISSUE.

Cooper CS, Pal K, Hewer A, Grover PL, Sims P
Chester Beatty Res. Inst., Inst. Cancer Res., Royal Cancer Hosp., Fulham Road, London SW3 6JB, England
Carcinogenesis; 3(2):203-210 1982

The metabolism of 7,12-dimethylbenz[a]anthracene (DMBA), benzo[a]pyrene (BP) and benz[a]anthracene (BA) by epithelial cell aggregates and fibroblasts in culture has been investigated using mammary tissue obtained from female Wistar rats. The results show that (a) both types of mammary cells metabolize all three hydrocarbons into ether- and water-soluble derivatives; (b) the patterns of metabolites produced by epithelial cells and fibroblasts are similar but that fibroblasts form more of the water-soluble materials; (c) the major dihydrodiols formed are the 8,9-dihydrodiols of BA and DMBA and the 7,8-and 9,10-dihydrodiols of BP; (d) all three hydrocarbons are metabolized to form products that bind covalently to protein but only the potent carcinogens BP and DMBA are metabolized to form derivatives that react covalently with DNA; and (e) the chromatographic profiles of the hydrocarbon-deoxyribonucleoside adducts formed in epithelial cells treated with either BP or DMBA are similar to those obtained in analogous experiments with fibroblasts. (Author abstract) (50 Refs)

43. DETECTION OF DUCTAL DYSPLASIA IN MAMMARY OUTGROWTHS DERIVED FROM CARCINOGEN-TREATED VIRGIN FEMALE BALB/C MICE.

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Cancer Res; 42(5):1753-1760 1982

These studies were undertaken to determine if altered growth potential of mammary epithelial cells could be detected in outgrowths derived from monodispersed mammary cells of virgin female BALB/c mice previously exposed to ionizing radiation or 7,12-dimethylbenz(a)anthracene (DMBA). Monodispersed mammary epithelial cells were obtained by enzymatic dissociation of mammary tissues of 12-wk-old virgin female BALB/c mice. Twenty-four hr prior to cell dissociation, donor animals were exposed to either 100 rads of gamma-ray irradiation, 0.25 mg of DMBA, or 0.075 mg of DMBA. Control donors were untreated. Mammary outgrowths were derived by injecting cells into the gland-free mammary fat pads of 3-wk-old virgin female BALB/c mice. Ten wk after the injection, the outgrowths were examined and classified. The data indicated that treatment of donor animals with either gamma-radiation or DMBA increased the frequency of ductal lesions over control levels. Both the frequency and severity of the lesions depended on the number of cells which were injected. When outgrowths were derived by injection of 10(5) cells into the gland-free fat pads, only a few severe lesions were detected. In outgrowths derived from 10(4) cells, less severe lesions (Class I lesions) were common in all groups and occurred in approximately 10 to 15% of the outgrowths. The frequency of severe (Class II and III) ductal dysplasia, however, was increased by treatment in these groups, occurring in 4.5% of control outgrowths in 15.6, 14.9, and 14.3% of the outgrowths derived from donor cells treated with 100 rads gamma-rays, 0.075 mg DMBA, and 0.25 mg DMBA, respectively. Thus, these data indicated that ductal dysplasias were more common and more severe in outgrowths derived from 10(4) rather than 10(5) cells. The ductal lesions observed in this study resembled both morphologically and histologically ductal abnormalities which have been associated with the pathogenesis of mammary carcinoma in both rats and mice. (29 Refs)

44. DIFFERENCES IN VASCULAR PATTERN BETWEEN THE SPONTANEOUS AND THE TRANSPLANTED C3H MOUSE MAMMARY CARCINOMA.

Falk P
Medical Res. Council Cyclotron Unit, Hammersmith Hosp., Ducane Road, London W12, England
Eur J Cancer Clin Oncol; 18(2):155-165 1982

The transplanted C3H tumor differs from the spontaneous in its multi-focal origin and in its increasing loss to differentiation. Loss of differentiation is principally important in that even the partial branching into lobes, which occurs in the spontaneous tumor, is lose and that the parenchyma no longer consists of single-layered and multi-layered tubules, as in the spontaneous tumor, but of multi-layered only. Absence of branching removes the interlobular pressures, which in spontaneous tumors lead to infarction of the efferent vessels and sinus formation. Consequently sinuses are absent from the transplanted tumor and the circulation is thereby improved. In contrast, since the vascular pattern of the spontaneous tumor is preserved and capillaries do not penetrate into the multi-layered tubules, although these have developed into solid cylinders, the diffusion pathway of oxygen is extended, resulting in necrosis at their cores. Accumulating necrotic fluid is at first removed by lymphatics, but subsequently invades the efferent vascular system. These changes are reflected in the pattern of tumor growth and in the radiation responses. (Author abstract) (9 Refs)

45. BREAST CARCINOMA WITH MULTINUCLEATED REACTIVE STROMAL GIANT CELLS. A STUDY OF THE CYTOLOGY, HISTOLOGY, ULTRASTRUCTURE, AND IMMUNOCYTOCHEMISTRY OF TWO CASES.

Bertrand G, Bidabe M, Bertrand A
Laboratoire d'Anatomie et de Cytologie Pathologiques, Centre Paul-Papin, 2, rue Moll, 49000 Angers, France
Arch Anat Cytol Pathol; 30(1):5-9 1982

Two cases of breast carcinoma with multinucleated reactive stromal giant cells are reported. The first patient, a 46-yr-old unmarried woman, presented with a nodule 2 cm in diameter on her right breast. Cytopuncture demonstrated the association of multinucleated giant cells and carcinomatous elements. Radiotherapy followed by mastectomy was successful in removing all elements of the tumor and at 4.5 yr postsurgery there was no apparent recurrence or metastases. A 47-yr-old mother of four children presented with a 2 cm nodule on her right breast. A history of recent trauma to the area was noted. Cytopuncture showed the presence of carcinomatous cells and giant multinucleated cells. Tumor excision and axillary curettage led to the discovery of a small partially metastasized ganglion. Diagnosis was made on the discovery of a large number of multinucleated giant cells associated with carcinomatous cells. The multinucleated cells represented the most important quantitative element of the diagnosis. The macrophage origin of the giant cells was confirmed by ultrastructural study but no macrophage activity could be demonstrated. Macroscopically, the tumor nodules presented a retracted appearance which was typically carcinomatous but the color was ochre which was very unusual. (16 Refs) (In FRE)

46. CYCLIC BIOLOGICAL EXPRESSION IN MOUSE MAMMARY TUMORS.

Kiang DT, King M, Zhang HJ, Kennedy BJ, Wang N
Section Medical Oncology, Dept. Medicine, Univ. Minnesota Medical Sch., Minneapolis, MN, 55455
Science; 216(4541):68-70 1982

Biological characteristics were assessed in GR mouse mammary tumors during 22 serial transplantations. Although unidirectional progression from hormone dependency to independency was observed, other biological markers such as progesterone receptors, polyploid frequency, and thymidine kinase activity demonstrated cyclic phenomena every fourth to sixth transplant generation, suggesting the continued presence of regulatory mechanisms among various cell subpopulations. (Author abstract) (13 Refs)

47. IMPLEMENTATION OF MICROMETHODS TO RESOLVE PROBLEMS OF HUMAN BREAST TUMOR HETEROGENEITY IN ANALYSIS OF CYCLIC 3':5'-NUCLEOTIDE PHOSPHODIESTERASE.

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Cancer Res; 42(5):1661-1668 1982

Individual human infiltrating ductal carcinomas and fibroadenomas were sectioned frozen to yield an alternating sequence of stained and lyophilized material. Stained preparations were used as references permitting microdissection of regions of tumor involvement in the corresponding dried sections. Tissue quantities of 5 to 25 ug dry weight were incubated under mineral oil in reaction volumes of 5 ul and analyzed for cyclic adenosine 3':5'-monophosphate phosphodiesterase (PDE). The observed affinity constants for the 27,000 x g soluble PDE from benign tumors were 4.7 and 49.9 uM, while those for malignant tumors were 6.3 and 28.5 uM. The soluble enzyme of both tumor types eluted in three peaks on DEAE-Sephacel microcolumns. Both tumor types possessed a PDE activator eluting at 350 mM NaCl, although endogenous PDE activities were unaffected by additions of either this activator or 200 uM ethylene glycol bis(beta-aminoethyl ether)N,N,N',N'-tetraacetic acid. Individual microsections of benign tumors contained total PDE levels two-fold higher than those of malignant tumors. Homogenates prepared from pooled microsections of the same tumors possessed only one-half of the total activity. Differential losses of enzyme in various preparation schemes as well as the use of tumor samples differing in cell density were suggested to account for some of the apparently conflicting literature values for breast tumor PDE. (Author abstract) (27 Refs)

48. INTEGRAL MEMBRANE GLYCOPROTEINS RELATED TO CELL-SUBSTRATUM ADHESION IN MAMMALIAN CELLS.

Damsky CH, Knudsen KA, Buck CA
Wistar Inst. Anatomy and Biology, Philadelphia, PA, 19104
J Cell Biochem; 18(1):1-13 1982

Goat antisera were raised against surface membrane-derived material from baby hamster kidney cells (BHK21/C13), a transformed line derived from cell line (C13/B4), and mouse mammary tumor epithelial cells (BALB/c MT2). The antisera to the hamster cell lines (anti-M) and the MT2 cells (anti-GP) disrupted cell-substrate adhesions in cultures of their respective cell types. An antibody blocking assay was used to isolate adhesion-related glycoproteins (GP) from non-ionic detergent (Nonidet NP40) extracts of each cell type. In each case, the product was a restricted population of GPs (mol wt about 120,000-160,000). Each GP fraction blocked the disruption of adhesion induced by the goat antiserum on either cell type (hamster kidney or mouse mammary tumor). The antisera were capable of disrupting cell-substratum adhesion of a large number of cell types and species sources. Antibody-blocking activity was detected in partially purified extracts of a variety of cultured cell types. In addition to similar substrate-associated GPs (eg, fibronectin) and cytoskeleton-associated proteins (eg, alpha-actinin and vinculin), cells from different tissues and different species apparently contained a relatively conserved class of integral membrane GPs involved in cell-substrate adhesion. (29 Refs)

49. A SIMULTANEOUS STUDY OF FIVE MARKERS IN 80 CASES OF BREAST CANCER. CARCINO-EMBRYONIC ANTIGEN (CEA), FERRITIN BETA2, MICROGLOBULIN, (BETA M), SUB-UNIT BETA OF CHORIONIC GONADOTROPHIN HORMONE (BETA CGH) AND ALPHA FETOPROTEIN (AFP).

Fourrier E, Kadouche J, Mignot L, Reynier J, Gorins A, Rochet Y, Trevoux R, Gavel M
Centre des Maladies du Sein, Hopital Saint-Louis, 38, rue Bichat, F 75010 Paris, France
Gynecologie; 32(4/5):385-390 1981

Pathological levels of CEA, ferritin (FT), microglobulin (beta M), (CGH), and alpha fetoprotein (AFP) were compared in various stages of breast cancer (80 cases). When the pathologic level of CEA was set at 2.5 nanograms (nanog)/ml, there were positive results in 63% of the cases at diagnosis, 95% of the metastasized cancers, and 42% of the postoperative cases. When the pathologic level of CEA was set at 4 nanog/ml, the percentages of positive cases were 35%, 91%, and 35% respectively. In all cases, the highest positive values were obtained with CEA and FT. The value of beta M was more limited, and CGH and AFP provided very little information. In 18 metastasized cases which were treated with chemotherapy, CEA assays evolved along parallel lines with the clinical course of the disease in 16 cases and in 2 cases, levels of CEA increased while the disease seemed stable. FT evolved along clinical lines in 17 cases, but levels increased in 1 case which seemed to be in regression. The other assay results did not correlate in any significant way with clinical course of the disease. Based on the results of this study, it is recommended that CEA and FT be used to monitor the progress of patients who have been surgically treated for breast cancer and are undergoing adjvant therapy. (15 Refs) (In FRE)

50. ISOELECTRIC FOCUSING OF OESTRADIOL RECEPTOR PROTEIN FROM HUMAN MAMMARY CARCINOMA - A COMPARISON WITH DEXTRAN COATED CHARCOAL ASSAY.

Lloyd EJ, Barnes DM, Skinner LG
MRC Toxicology Unit, Woodmansterne Road, Carshalton, Surrey SM5 4EF, England
J Steroid Biochem; 16(2):239-244 1982

Isoelectric focusing (IEF) of receptor protein in polyacrylamide gel and dextran-coated charcoal (DCC) receptor assays were compared for ability to detect specific estradiol-17beta receptor protein in breast tumor tissue. When IEF was performed on 29 selected cytosols without partial trypsin digestion, 83% of the findings correlated with results obtained with DCC. When trypsin digestion was included in 32 cytosols, 97% agreement on the receptor status was achieved. Quantitative analysis of the positive results demonstrated that those obtained by IEF gave significantly lower values than DCC analysis: the correlation coefficient was 0.88. When 40 freeze-dried samples weighing between 4-55 mg were analyzed by IEF and the results compared with those obtained with DCC, 87% agreement was achieved. With Tru-Cut biopsy samples taken immediately before mastectomy (2-34 mg), qualitative agreement was 88% between IEF and DCC, with no significant difference between the quantitative results of the two methods. A correlation coefficient of 0.62 was obtained from the 15 positive results. Both IEF and DCC methods can measure receptor concentrations as low as 5 femtomoles/mg protein; however, the IEF results were obtained on as little as 1/10th the amount of material. (12 Refs)

51. ASSAY OF ESTRADIOL RECEPTORS IN HUMAN BREAST CARCINOMAS USING THE GAMMA EMITTING LIGAND 16ALPHA[125I]IODOESTRADIOL.

Duffy MJ
Dept. Nuclear Medicine, St. Vincent's Hosp., Dublin 4, Ireland
J Steroid Biochem; 16(2):343-344 1982

The use of 16alpha[125I]iodoestradiol to assay estrogen receptor (ER) in human breast carcinoma was investigated. A constant amount of cytosol was incubated at five different concentrations of radiolabeled estradiol overnight at 4 C, and nonspecific binding was measured with parallel incubations in the presence of 100-fold excess unlabeled diethylstilbestrol (DES). Excess unlabeled estradiol and DES were the most potent inhibitors of binding, estrone and estriol were less potent, and testosterone, progesterone, and cortisol were ineffective. The affinity of iodoestradiol for breast tumor ER was similar to that of tritiated estradiol in 19 carcinoma cytosols. Good agreement was found between results using tritiated and iodoestradiol as ligands (correlation coefficient = 0.97). Twelve tumors contained less than 50 femtomoles ER by both ligands. Good agreement was observed between the use of a single saturating concentration of 5 nanoM iodoestradiol and the Scatchard plot analysis using the same ligand (correlation coefficient = 0.97). Advantages of using a gamma-emitting ligand for the assay of ER in breast tumor tissue are listed. (4 Refs)

52. IMMUNOHISTOCHEMICAL LOCALIZATION OF ESTROGEN RECEPTORS IN HUMAN MAMMARY CARCINOMA USING ANTIBODIES TO THE RECEPTOR PROTEIN.

Raam S, Nemeth E, Tamura H, O'Briain DS, Cohen JL
Oncology Lab., Tufts Univ. Medical Cancer Unit, Lemuel Shattuck Hosp., 170 Morton St., Boston, MA, 02130
Eur J Cancer Clin Oncol; 18(1):1-12 1982

An immunofluorescent method has been developed for localizing estrogen receptors (ER) in frozen sections of human breast cancer biopsies which utilizes the biochemically well-characterized antibodies to the cytoplasmic ER of human breast cancer produced in rabbits. Frozen sections of 16 breast cancer biopsies, in which the receptor content has been quantified using dextran-coated charcoal assay (DCC technique), were used to study the localization of ER. Two aspects of ER detection, namely 'estrogen-binding' and ability to react with the homologous antibodies, have been analyzed and the results compared with those of DCC technique. Fluorescent labeled estrogen method (F-E2) of Pertschuk was utilized to detect the distribution of estrogen binding proteins and the indirect immunofluorescent (IM-AR) method using antireceptor antibodies to assess the antigenic sites of the receptor protein. In addition to the comparison of the results of three techniques, DCC, IM-AR and F-E2, for ER detection, a procedure for processing the frozen sections, which enables the study of estrogen binding characteristic as well as the antigenic reactivity of the receptor molecules, is described. (Author abstract) (10 Refs)

53. HISTOCHEMICAL DETECTION OF OESTROGEN RECEPTORS: A PROGRESS REPORT.

Penney GC, Hawkins RA
Univ. Dept. Clinical Surgery, Royal Infirmary, Edinburgh, Scotland
Br J Cancer; 45(2):237-246 1982

Four albumin conjugates of estradiol, labeled with fluorescein or peroxidase to permit visualization under light or fluorescence microscopy, were synthesized. These were used to examine the feasibility of identifying estrogen binding in frozen section by two published histochemical techniques. In a variety of experimental tissues and human breast cancers, binding of the estrogen conjugates was demonstrable, but it appeared nonspecific (ie, rarely displaceable by competitor) and unrelated to estrogen receptor (RE) status of the tissue as determined biochemically by assay with dextran-coated charcoal. Investigation of the fate of the RE through the various steps of a histochemical assay, demonstrated major losses of RE from unfixed tissue or after tissue fixation. The RE also exhibited a 10-50-fold poorer affinity for the conjugates synthesized than for estradiol-17beta and, at the concentrations of conjugate routinely used in histochemical assays, it seems likely that considerable nonspecific binding takes place. These factors may combine to make it (1) difficult to implement such histochemical assays and (2) unlikely that the RE is being detected. (Author abstract) (21 Refs)

54. EVIDENCE FOR THE ORIGIN OF THE UNOCCUPIED OESTROGEN RECEPTOR IN NUCLEI OF A HUMAN BREAST-CANCER CELL LINE (MCF-7).

Geier A, Haimsohn M, Lunenfeld B
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Biochem J; 202(3):687-691 1982

The origin of the unoccupied nuclear estrogen receptor (Rn) was studied. Three working hypotheses were investigated. (a) Rn is a dissociation product of the estrogen occupied nuclear receptor (ERn). (b) ERn is only partially occupied, so that additional binding may occur at 0 C (the temperature at which estradiol saturates unoccupied sites). (c) Rn is derived from the penetration of unoccupied cytoplasmic receptor (Rc) into the nucleus. The MCF-7 cell line was used as a model in the present investigation. The amount of unoccupied receptors was measured by saturation with 7.5 nM-[3H]estradiol at 0 C, whereas the occupied receptors were measured by exchange at 30 C. The cells at preconfluency were exposed to a meduim fortified with 10 nM-[3H]estradiol for 1 hr, washed and cultured up to 5 days in fresh growth medium. The distribution of estradiol receptors was determined before exposure and during the following 5 days. After 1h exposure only ERn was found in the nuclear fraction. Thereafter ERn declined continuously so that on day 5 it approached 15% of its value measured 1 hr after exposure. Although after 3 days about 80% of ERn disappeared on Rn appeared, which contradicts hypotheses (a) and (b). On Day 4 Rn and Rc appeared simultaneously. The appearance of Rn and Rc was not prevented by culturing the cells in an estrogen-free medium, supporting hypothesis (c). Exposure of cells to increasing concentration of [3H]estradiol (0.1-10 nM) for 1 hr resulted in a parallel increase in ERn without increasing the amount of unoccupied binding sites, which contradicts hypothesis (b). The present study supports the hypothesis (c), ie, Rc may also penetrate the nucleus without binding to estradiol. (Author abstract) (18 Refs)

55. ESTRONE RECEPTOR FORMATION DURING THE PROCESSING OF ESTRADIOL-RECEPTOR COMPLEX IN MCF-7 CELLS.

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Cancer Res; 42(5):1967-1974 1982

Human breast cancer cells (MCF-7) contain separate estrogen receptors specific for either 17-beta-estradiol or estrone. Utilizing optimum conditions for the protamine sulfate assay, it has been possible to demonstrate both receptors in the 0.6 M KCl extract of nuclei and in the cytosol. Similarly, in the exchange assay, high-affinity low-capacity binding sites for 17beta-estradiol and estrone have been found in the salt-extracted nuclear residue. Dissociation constants and binding capacities were demonstrated for either receptor in the absence of the other or, when both receptors were present, a saturating amount of the other estrogen was added to the assay mixture. Specificity was demonstrated by the inability of estrone to compete with 17beta-[2,4,6,7-3H]estradiol for the 17beta-estradiol receptor at molar excesses less than 10-fold. Likewise, there was no inhibition of [6,7-3H]estrone binding to its receptor by molar excesses of 17beta-estradiol below 100-fold. Other steroid hormones were very weak competitors of [6,7-3H]estrone. The quantitative relationships of these two estrogen receptors were shown to fluctuate in the various cellular compartments following incubation of MCF-7 cells with 10(-8) M 17beta-estradiol. This level of 17beta-estradiol elicited the translocation of all detectable cytosolic E2R to the nucleus, where the salt-resistant 17beta-estradiol disappeared and 40% of the extractable 17beta-estradiol-binding capacity was lost. Simultaneously, the E1R which remained in the nuclear residue appeared in the nuclear extract, and ultimately this receptor accumulated in the cytosol. The estrone-binding capacity which appeared following the processing of E2R nearly equalled the loss of 17beta-estradiol binding sites per cell. Concentrations of 17beta-estradiol which elicited the greatest processing of E2R in these incubations brought about the appearance of max levels of E1R in MCF-7 cells. Processing would appear to involve the formation of estrone receptor (E1R) in the salt-resistant nuclear compartment followed by the accumulation of E1R in the cytosol. (40 Refs)

56. MICROASSAY OF HORMONAL RECEPTORS BY NEEDLE BIOPSY IN HUMAN BREAST LESIONS AND TUMORS. DETERMINATION OF ESTROGEN RECEPTORS.

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Institut Gustave-Roussy, Rue Camille-Desmoulin, 94800 Villejuif, France

Biomedicine; 34(3):153-160 1981

Estrogen receptors measurement was assayed in human mammary tumors as well as corresponding fine needle aspiration biopsies (95 cases). Correlations between these two determinations were highly significant just as correlations between aspiration biopsies of the same tumor. Some factors may disturb the quality of aspiration biopsy results particularly: a low number of tumoral cells expressed by the cell density, ratio: sample weight-cytosol volume lower than 1/17 corresponding to a too great dilution, a sample weight lower than 20 mg. (Author abstract) (13 Refs) (In FRE)

57. CELLULAR LOCALIZATION OF ESTROGEN BINDING SITES IN HUMAN BREAST CANCER.

Hanna W, Ryder DE, Mobbs BG

Dept. Lab., Women's Coll. Hosp., 76 Greenville St., Toronto, Ontario M5S 1B2, Canada

Am J Clin Pathol; 77(4):391-395 1982

Biopsy specimens from 52 consecutive cases of primary human breast cancer were collected over a period of 7 mo and included in a study for histochemical localization of estrogen binding sites (EBS), using a fluorescein labeled Estradiol conjugate. Cryostat frozen sections from each tumor were examined to determine the localization of the tracer and to evaluate the percentage of positive cells in a given tumor. Results are correlated with the values of the biochemical assay for the estrogen receptor (ER) protein done on the same tumor. The localization of EBS by a tracer is a simple technique that can be done and interpreted in any surgical pathology laboratory. It was concluded that this method could be a valuable supplementary technique to the biochemical assay; allowing more accurate selection of patients and prediction of their response to endocrine therapy. Clinical follow-ups are extremely necessary to evaluate the suitability and the accuracy of the technique in choosing breast cancer patients for endocrine manipulation. (Author abstract) (17 Refs)

58. RESEARCH ON ESTROGEN AND PROGESTERONE RECEPTORS IN HUMAN BREAST CANCER.

Kakuta E
Second Dept. Surgery, Tokushima Univ. Sch. Medicine, Tokushima-shi, Japan
Nippon Gan Chiryo Gakkai Shi; 16(7):1408-1416 1981

Estrogen receptors (ER) and progesterone receptors (PR) were measured with the aid of gel-filtration in the cytosols of human breast cancer tissues from 120 patients with primary breast cancer and 32 with recurrent breast cancer. The ER and PR were measured at the same time in surgical specimens from 53/120 patients with the primary cancer and 22/32 with the recurrent cancer. ER were present (ER+) in 43.1% of the cases and PR were present (PR+) in 25%. Differences in the frequencies of ER+ and PR+ were not related to the stage or histological type of the cancer or to the pre- or postmenopausal status of the patients. PR+ findings were observed significantly more often in tissues that were also ER+ than in those that were ER negative (ER-). Results indicating the presence or absence of ER and PR in primary and metastatic tumor nests were often consistent whether or not ER and PR were measured synchronously. Effectiveness of endocrine therapy was observed in 71.4% of the ER+ patients, 5.6% of the ER-, 4/5 PR+, and 3/14 PR-. It was concluded that selection of patients who are likely to have effective endocrine therapy for breast cancer may be enhanced by measuring ER in breast cancer tissues. (23 Refs) (In JPN)

59. VARIANT T47D HUMAN BREAST CANCER CELLS WITH HIGH PROGESTERONE-RECEPTOR LEVELS DESPITE ESTROGEN AND ANTIESTROGEN RESISTANCE.

Horwitz KB, Mockus MB, Lessey BA
Dept. Medicine, Univ. Colorado Health Sciences Center, Denver, CO, 80262
Cell; 28(3):633-642 1982

In target tissues for estrogen, including breast cancer cells, the synthesis of progesterone receptors (PRs) is controlled by estradiol acting through estrogen receptors (ERs). We describe studies with T47D human breast cancer cells, whose PRs are not regulated by estradiol, though present in extraordinary amounts (300,000 sites per cell). These cells have no ERs sedimenting at 8S on sucrose density gradients, and no unfilled cytoplasmic or nuclear ERs; some apparently hormone-filled nuclear sites, with KD approx or equal to 0.7 nM, can be demonstrated by exchange. The nuclear ER sites are not processed after estradiol treatment. Nafoxidine, however, doubles nuclear estrogen binding in 6 hr, in a cycloheximide-insensitive step that may represent a reversal of processing. T47D cells are profoundly resistant to estrogens and antiestrogens; estradiol does not stimulate PRs, and nafoxidine concentrations that are cytotoxic to ER-positive cells have no effect on cell growth or on PR levels. Yet the PRs are normal by several criteria, and they can be stoichiometrically translocated to, and extracted from, nuclei in the first 3 min after progesterone addition. If progesterone treatment exceeds 10 min, rapid nuclear turnover prevents quantitative PR recovery. Cytoplasmic PRs are replenished in 10 to 24 hr, and this cycloheximide-sensitive step is also estrogen- and nafoxidine-resistant. However, despite their insensitivity to estradiol or antiestrogen, PRs are not constitutively synthesized; 5-bromodeoxyuridine and sodium butyrate can selectively inhibit PR production. Thus, since PRs retain some characteristics of inducible proteins, the persistent nucelar estrogen-binding sites may be stimulating PRs continuously, even in the absence of exogenous estradiol. (Author abstract) (45 Refs)

60. DOWN-REGULATION OF INSULIN RECEPTORS IN PRIMARY CULTURES OF R3230 AC RAT MAMMARY ADENOCARCINOMA CELLS.

Sorge LK, Hilf R
(c/o Hilf) Dept. Biochemistry, Box 607, Univ. Rochester Medical Center, 601 Elmwood Ave., Rochester, NY, 14642
Endocrinology; 110(4):1155-1163 1982

Binding of insulin and Concanavalin A to primary cell cultures of the R3230AC rat mammary adenocarcinoma was studied as a function of time in culture. As the culture became confluent, the amount of insulin binding per cell increased with culture time and reached a plateau, whereas the binding of Con A to surface glycoproteins decreased to 50% of the initial value. Exposure of confluent cultures to insulin at 37 C resulted in down-regulation of the cell surface insulin receptors. The decrease in insulin binding was related to the ambient insulin concentration and the decreased numbers of receptors per cell with no apparent alteration in their affinity. The maximal decrease in receptor number was 60-70%. Cell cultures degraded significant amounts of insulin at 37 C, but the addition of bacitracin to the culture medium decreased the amount of degradation and increased the extent of down-regulation at each insulin concentration. Porcine proinsulin was less effective than insulin in competing with 125I-labeled insulin and inducing receptor down-regulation. Down-regulation of insulin receptors did not require protein synthesis. The rate of insulin-induced receptor loss was much faster than the decrease in insulin binding due to inhibition of protein synthesis by cycloheximide. The estimated half-life of the insulin receptor was 10.5 hr. Down-regulation of insulin receptors was reversible; regeneration of receptors to 50% of control levels occurred approx 9.6 hr after the removal of insulin and required protein synthesis. The results indicate that these mammary tumor cells retain the ability to regulate their insulin receptors. (Author abstract) (53 Refs)

61. FIBRONECTIN IN HUMAN BREAST TUMORS. OPTICAL STUDIES IN VITRO AND IN VIVO ABOUT 19 CASES.

Noel P, Faucon M, Thevenin MA
Unite de Morphologie Cellulaire et Tissulaire, Centre Leon Berard, 28 rue Laennec, F 69373 Lyon Cedex 2, France
Ann Pathol; 2(1):41-48 1982

Fibronectin attracted so much interest in the last yr because of the discovery of its decrease or disappearance on the cell membrane of transformed malignant cells. The aim of this work was to study the behavior of the breast human tumors to know if the progressive loss of fibronectin followed by its complete disappearance can be considered as a morphological marker correlated with the clinical passage from benignity to malignancy. The authors studied fibronectin in 19 cases of human breast tumors (9 malignant tumors, 9 benign tumors, and 1 case of the so-called human normal breast tissue) by indirect immunofluorescence on tumor biopsy sections (in vivo) and tumor-cell cultures (in vitro). The interest of fibronectin staining was based upon its decrease or disappearance in the cell membrane of malignant transformed cells; the basement membrane rupture is an important proof of the establishment of malignancy in human pathology. The results in vivo were as follows: In all the cases of fibroadenomas, the presence of fibronectin in the basement membrane of galactophores and adjacent myoepithelial cells was noted. These results were found in normal breast tissue samples. In fibrocystic disease, the above mentioned model was present but different: the fluorescent staining of the basement membrane by the fibronectin was limited in some parts of the membrane and had an irregular thickness. In malignant breast tumors such as infiltrating carcinomas, we noted in all cases the disappearance of fibronectin staining on basement membrane (9 cases): in several samples a lamellar aspect of the basement membrane was noted allowing clusters of malignant cells to invade the stroma. The results 'in vitro' emphasized both stages of intracytoplasmic fibronectin production and extracytoplasmic excretion: the results were different from those above mentioned 'in vivo'. (Author abstract) (10 Refs) (In FRE)

62. ASSOCIATION OF PLASMINOGEN ACTIVATOR ACTIVITY AND STEROID RECEPTORS IN HUMAN BREAST CANCER.

Thorsen T
Hormone Lab., Univ. Bergen Sch. Medicine, Bergen, Norway
Eur J Cancer Clin Oncol; 18(2):129-132 1982

Plasminogen activating activity (PAA) has been determined in 105 human breast cancer cytosols with a colorimetric assay. PAA has been related to steroid receptors in the same cytosols. A strong positive correlation between PAA and progesterone receptor levels was found (Spearmans coefficient of rank correlation, $R = 0.74$, p less than 0.001). PAA discriminates between progesterone receptor-positive and -negative tumors, irrespective of estradiol receptor content. It is suggested that PAA is a marker of functional estradiol receptor and that fibrinolytic activity may be a causative factor in the low metastatic potential of progesterone receptor-positive tumors. (Author abstract) (25 Refs)

63. ELASTIN DEGRADATION BY PROTEASES FROM CULTURED HUMAN BREAST CANCER CELLS.

Kao RT, Wong M, Stern R
Dept. Pathology, Univ. California San Francisco, San Francisco, CA, 94143
Biochem Biophys Res Commun; 105(1):383-389 1982

The human breast tumor cell lines ZR75-1, ZR75-30, ZR75-31A, and MFC-7 were found to exhibit elastinolytic activity in culture. DEAE-cellulose chromatography was used to separate the elastase-like activity of ZR75-31A cells into three different proteases; two were identified as serine proteases and one a metalloprotease based on inhibition studies with protease inhibitors. Each existed in an inactive form and required trypsin pretreatment for activity. The enzymes may be involved in modulation and turnover of the elastin-containing desmoplastic reaction found in most human breast cancers. (14 Refs)

64. PLASMINOGEN ACTIVATORS IN NEOPLASTIC CELLS.

Goloborod'ko OP, Veremeenko KN
A. I. Kolomiichenko Res. Inst. Otolaryngology, Kiev, USSR
Eksp Onkol; 4(1):3-7 1982

Role of specific fibrinolytic enzymes in the carcinogenesis is reviewed. Invasiveness and metastatic spreading of malignant cells was shown to be associated with plasminogen activators (PA). Progressive increase of fibrinolytic activity in the culture medium of transformed cells is due to elevated secretion of PA. The rate of PA formation and the degree of fibrinolytic activity are correlated with the morphological criteria of malignant transformation. Elevated secretion of PA was also observed in cultured cells of human malignant tumors (giant cell lung cancer, brain cancer, ovarian cancer). Long-term cultures of malignant cells showed gradual loss of ability to secrete PA. Increased PA levels were observed in the patients with cancer of the brain, breast, stomach, endometrium, cervix uteri, and bladder. PA was detected in the nuclear and mitochondrial fractions of murine Ehrlich's ascites carcinoma cells. The mechanism of PA effect was shown to be associated with the changes of the properties of cell membranes and membrane enzymes. (55 Refs) (In RUS)

65. DEMONSTRATION OF LACTOPEROXIDASE IN PARAFFIN-EMBEDDED LACTATING BOVINE BREAST BY IMMUNOCYTOCHEMICAL TECHNIQUES.

Bussolati G, Gugliotta P, Papotti M
Istituto di Anatomia e Istologia Pathologica, Univ. Turin, Turin, Italy
J Histochem Cytochem; 30(5):477-480 1982

Immunocytochemical methods have been applied to the demonstration of lactoperoxidase (LP) in the lactating bovine breast. Trypsin digestion and a MAGIC procedure, using anti-LP serum and then LP solution in sequence, made the sensitive and specific demonstration of LP in formalin-fixed paraffin-embedded sections possible. Peroxidase of the breast has been shown to be inducible by estrogen stimulation and it is considered to be a possible marker of estrogen dependency in breast carcinomas. The present technique, applied to human tissues, even on fixed and embedded biopsies, might make possible the detection of LP in human breast cancers and, thereby, an evaluation of estrogen dependency of such cancers. (Author abstract) (16 Refs)

66. IMMUNOCHEMICAL STUDY OF ANDROGEN-BINDING BETA-GLOBULIN IN HEALTHY CONTROLS AND CANCER PATIENTS.

Terent'ev AA, Feshchenko SP, Tatarinov IuS
Dept. Biological Chemistry, N. I. Pirogov Second Medical Inst., Moscow, USSR
Biull Eksp Biol Med; 92(1):58-60 1982

Androgen-binding beta-globulin (ABBG) was assayed in blood sera and tissue extracts of healthy controls and cancer patients. Immunodiffusion and immunoelectrophoresis showed the presence of ABBG in extracts of the prostate and the sperm, but not in the blood sera, of the healthy controls. The ABBG was present in tumor tissue extracts of the patients with breast cancer, kidney cancer, stomach cancer, colonic cancer, brain cancer, or testicular cancer and in the blood sera of 50% of the cancer patients. Tests for cross reactions showed that the ABBG was not identical to antigens showing affinity to steroid hormones. (13 Refs) (In RUS)

67. ENZYMES OF COLLAGEN SYNTHESIS AND TYPE III PROCOLLAGEN AMINO-PROPEPTIDE IN SERUM FROM NIGERIANS WITH HEPATOCELLULAR CARCINOMA AND OTHER MALIGNANT DISEASES.

Bolarin DM, Savolainen ER, Kivirikko KI
(c/o Kivirikko) Dept. Medical Biochemistry, Univ. Oulu, SF-90220 Oulu 22, Finland
Int J Cancer; 29(4):401-405 1982

Serum immunoreactive prolyl hydroxylase protein (S-IRPH), galactosylhydroxylysyl glucosyltransferase activity (S-GGT) and the amino-terminal propeptide of Type III procollagen [S-Pro(III)-N-P] were studied in 24 patients with primary hepatocellular carcinoma, 18 with secondary liver neoplasms and 35 with other malignant diseases but no evidence of liver involvement; this latter group included 13 patients with Burkitt's lymphoma, 11 with breast cancer and 11 with other neoplasms. Control values were determined for 60 apparently healthy Nigerians. S-IRPH and S-GGT were above the upper normal limit, defined as the mean +2 SD of the controls, in all the patients with primary hepatocellular carcinoma and all but one with secondry liver neoplasms, whereas only one S-IRPH value and three S-GGT values exceeded this limit in the patients with other malignant diseases. The mean S-Pro(III)-N-P was even more elevated than S-IRPH and S-GGT in the primary and secondary liver neoplasm cases, but was also elevated in other malignant neoplasms; about one third of the patients with no evidence of liver involvement had a concentration exceeding the upper normal limit. A high correlation was found between the values for the three assays both in primary hepatocellular carcinoma and in the whole series of malignant diseases. The data suggest that primary and secondary malignant neoplasms of the liver have a high rate of collagen synthesis. The three assays may be of some value in the diagnosis of primary hepatocellular carcinoma and secondary liver involvement in other malignant diseases, and in monitoring the treatment provided. (Author abstract) (22 Refs)

REVIEWS AND OTHER RELATED STUDIES

68. HORMONAL RECEPTORS AND BREAST CANCER.

Basso L, Bertolotti MG
II Divisione di Medicina Generale, Ospedale Generale Provinciale Ente Ospedaliero 'S. Paolo', Savona, Italy
Arch Sci Med (Torino); 139(1):63-68 1982

Current aspects of hormonal receptors and hormones were reviewed under the following headings: hormonal receptor determination, estrogens, androgens, prolactin, insulin, glycocorticoids and progesterone, and present approach in therapy. The importance of mammary receptors in therapy of mammary cancer was stressed. (26 Refs) (In ITA)

69. SEX HORMONES AND RELATED COMPOUNDS, INCLUDING ORAL CONTRACEPTIVES.

Plotz EJ, Nocke W, Schander K, Patt V, Kaulhausen H
Dept. Obstetrics and Gynecology, Univ. Bonn, 5300 Bonn-Venusberg, W. Germany
Side Eff Drug Annu; (5):358-380 1981

Side effects of sex hormones and related compounds are reviewed. Hormonal replacement therapy is discussed with respect to conjugated estrogens, estrogen/progestogen combinations, estriol succinate, estradiol valerate, a combination of the two preceding drugs, intravaginally administered estrogens, and benefits vs risks. Treatment with sex hormones of breast and liver tumors, industrial exposure to steroid hormones used in oral contraceptives (OC), gall bladder disease, psychic changes, acute intermittent porphyria, prolactin secretion in cases of pituitary adenoma and in lactating women, injectable and implanted steroidal contraceptives, low-dose combination OC, progestogen-only OC, combination of estrogens with cyproterone acetate, hormonal contraceptives and vitamins, teratogenicity, antiestrogens, and antiandrogens are each discussed. (159 Refs)

70. TUMORAL IMMUNOLOGY III. IMMUNOLOGY IN MAMMARY CANCER.

Crisci CD
Catedra de Neumonologia, Alergia e Inmunologia Clinica, Facultad de Ciencias Medicas, U.N.R., Rosario, Argentina
Rev Fac Cienc Med Univ Nac Rosario; 14(2):34-45 1981

Immunology in mammary cancer was reviewed under the following headings: antigen associated with tumors (AAT) in mammary cancer (MC), carcinoembryonic antigen (CEA), response to the AAT in MC (humoral and cellular responses; blocking factors), evaluation of the immune (IM) system in MC (subpopulations of lymphocytes, lymphoproliferative response to mitogens, delayed hypersensitivity in vivo, and immunoglobulins), and evaluation of IM state and of levels of CEA in MC in relation to tumoral spreading and evolution after surgery and radiotherapy (IM state at time of diagnosis, IM state immediately after the surgery, evolution of the IM state after treatment, and CEA). (242 Refs) (In SPA)

71. CAUSES OF LEUKEMIAS AND CANCER: RECENT PROGRESS.

Bernard J
bd. de Perolles 53, 1700 Fribourg, Switzerland
Rev Med Suisse Romande; 102(1):95-103 1982

Roles of viruses, radiation, and toxic chemical substances in the development of cancer are discussed. Burkitt's lymphoma (BL), a B-cell lymphoma predominantly localized in facial bones and found most frequently in certain areas of Africa, was one of the first cancers to be related to a virus, Epstein Barr virus (EBV). EBV virus and its antibodies are found in BL patients. EBV virus, the infective agent in mononucleosis, has been shown to cause BL in marmosets. BL shows high correlations with geographic areas with levels of malaria, with chromosome translocation 8:14, and with lower socioeconomic groups. Viruses have also been implicated in cervix cancer (herpes virus), liver cancer (hepatitis B), and Hodgkin's disease. Evidence of radiation-induced cancers has been gained from studies of physicians, radiologists, and scientists exposed to radiation and of Hiroshima survivors. The relationship between radiation and cancer development is significant but varies among individuals. Dietary factors, such as tobacco (lung, bladder, and digestive cancers), alcohol (cirrhosis and liver cancer), and diet in general (high lipid diet and breast cancer) have been related to increased incidences of cancer. Leukemia has been observed in Hodgkin's disease patients treated with chemotherapy. A high incidence of lymphomas has been noted in patients who have undergone organ transplants. The role of heredity and geography in the etiology of cancer is discussed. (no Refs) (In FRE)

72. ROLE OF HORMONES IN THE ETIOLOGY AND PREVENTION OF ENDOMETRIAL AND BREAST CANCER.

Gambrell RD
Dept. Endocrinology, Medical Coll. Georgia, Augusta, GA, 30912
Acta Obstet Gynecol Scand [Suppl]; (106):37-46 1982

Although there is a slightly increased risk of endometrial cancer from estrogen therapy for menopausal women, progestogens given along with the estrogen significantly decrease the incidence of this malignancy to a rate lower than that of untreated women. Postmenopausal women predisposed to adenocarcinoma of the endometrium because of increased endogenous estrogens can be identified with the progestogen challenge test and treated with cyclic progestogens for 10 days each mo to prevent endometrial cancer. Oral contraceptives containing both estrogens and progestogens in each tablet are protective against developing adenocarcinoma of the endometrium, whereas the sequential birth control pills provided less protection. The incidence of breast cancer is significantly lower in both estrogen and estrogen-progestogen users than in postmenopausal women never using these hormones. In those women found to have breast cancer while using these hormones, the prognosis is better than that found in women never exposed to exogenous estrogens, most likely due to an earlier detection. No clear-cut pattern of either abnormal hormone production or milieu has been found in women with carcinoma of the breast. Oral contraceptives reduce the risk of benign breast disease and afford some protection from the subsequent development of breast cancer. The mortality rate from breast cancer developing in orel contraceptive users is significantly lower than that of the non-users. (Author abstract) (50 Refs)

73. TOXICITY AND METABOLISM OF ACRYLONITRILE.

Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland

Med Pr; 32(1):25-33 1981

Studies in experimental animals and in vitro culture on the toxic effects and metabolism of acrylonitrile (AN) are reviewed. AN was found to be mutagenic for certain strains of Salmonella typhimurium and Escherichia coli. Increased incidence of tumors of the mammary glands, stomach, peripheral nervous system and sebaceous glands of the auditory meatus was found in female rats inhaling AN for 52 wk compared with controls. (40 Refs) (In POL)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers; selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY AND METABOLISM OF ACRYLONITRILE.
Sapota A, Chmielnicka J
Zaklad Metabolizmu Substancji Toksycznych, Instytut Medycyny Pracy, ul. Teresy 8, 90-950 Lodz, Poland
Med Pr; 32(1):25-33 1981
In POL

2. A REVIEW OF THE GENOTOXICITY OF FOOD, DRUG AND COSMETIC COLOURS AND OTHER AZO, TRIPHENYLMETHANE AND XANTHENE DYES.
Combes RD, Haveland-Smith RB
Dept. Biological Sciences, Portsmouth Polytechnic, King Henry I St., Portsmouth, PO1 2DY, Hants, England
Mutat Res; 98(2):101-248 1982

3. CARCINOGENICITY OF AIRBORNE FINE PARTICULATE BENZO(A)PYRENE: AN APPRAISAL OF THE EVIDENCE AND THE NEED FOR CONTROL.
Perera F
Natl. Resources Defense Council, Inc., 122 East 42nd St., New York, NY, 10168
Environ Health Perspect; 42:163-185 1981

4. TOXICOLOGY OF N-NITROSO COMPOUNDS.
Coulston F, Olajos EJ
Albany Medical Coll., Albany, NY, 12208
Ecotoxicol Environ Saf; 6(1):89-96 1982

5. CRITICAL REVIEW OF THE MUTAGENIC AND OTHER GENOTOXIC EFFECTS OF DIRECT COAL LIQUEFACTION.
Kimball RF, Munro NB
Oak Ridge Natl. Lab., Oak Ridge, TN
Critical Review of the Mutagenic and Other Genotoxic Effects of Direct Coal Liquefaction. Available from National Technical Information Service, Springfield, VA, as DE81027859:, 216 pp., 1981.

6. CARCINOGENICITY AND ITS EFFECT ON MEDICINAL RESEARCH PROGRAMS IN THE USA.
Van Ryzin RJ
Pharmaceutical Res. and Development, Sandoz, Inc., East Hanover, NJ, 07936
Med Res Rev; 2(2):153-166 1982

7. ANTIPROTOZOAL DRUGS (SIDE EFFECTS).
Nir I
Dept. Pharmacology and Experimental Therapeutics, The Hebrew Univ., Hadassah Medical Sch., Jerusalem, Israel
Side Eff Drugs Annu; (5):278-284 1981

8. DRUGS USED IN TUBERCULOSIS AND LEPROSY (SIDE EFFECTS).
Elis J
Inst. Pharmacology, Czechoslovak Acad. Sciences, Albertov 4, Prague 2, Czechoslovakia
Side Eff Drugs Annu; (5):290-297 1981

9. SEX HORMONES AND RELATED COMPOUNDS, INCLUDING ORAL CONTRACEPTIVES.
Plotz EJ, Nocke W, Schander K, Patt V, Kaulhausen H
Dept. Obstetrics and Gynecology, Univ. Bonn, 5300 Bonn-Venusberg, W Germany
Side Eff Drug Annu; (5):358-380 1981

RADIATION CARCINOGENESIS

10. NEPTUNIUM - THE NEGLECTED ACTINIDE: A REVIEW OF THE BIOLOGICAL AND ENVIRONMENTAL LITERATURE.
Thompson RC
Biology Dept., Pacific Northwest Lab., Richland, WA, 99352
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PREVALENCE OF BREAST CANCER IN HUMAN POPULATIONS

1. FAMILIAL BREAST CANCER IN ICELAND.

Tulinius H, Day NE, Bjarnason O, Geirsson G, Johannesson G, De Gonzalez MA, Sigvaldason H, Bjarnadottir G, Grimsdottir K
Icelandic Cancer Registry, P.O. Box 523, 121 Reykjavik, Iceland
Int J Cancer; 29(4):365-371 1982

Women who have relatives known to have had breast cancer are at an increased risk of getting the disease compared with the general population. On the basis of an extensive collection of family trees of women with breast cancer, the magnitude of this increase in risk is computed. Previously published results on other breast cancer risk factors are drawn upon and it has been possible to take account of some of these eg, age, decade of birth, age at first childbirth and parity in the risk estimates. The relative risk with such adjustment is found to be 2.59 for mothers and 2.56 for sisters. (Author abstract) (17 Refs)

2. CANCER IN THAILAND: LESSONS FOR CANCER CONTROL.

Miller DG, Somboocharoen S
Strang Clinic, Preventive Medicine Inst., 55 East 34th St., New York, NY, 10016
Prev Med; 11(2):232-239 1982

Patterns of neoplasia encountered in Thailand are discussed and the implications of the cancer control program of Thailand for cancer control in the United States are reviewed. Cancer was the sixth most common cause of mortality in Thailand in 1970. By 1977 it ranked third after accidents and cardiopulmonary disease. Cancer patients in Thailand, as elsewhere, utilize a disproportionately large fraction of available medical care. In 1975, liver, lung, and stomach in the male and cervical, breast, and liver in the female were the most common malignancies reported by 85 collaborating rural hospitals. In contrast, the most common cancers in urban Thais included nasopharyngeal, oral and lung in the male, and cervical, oral and lung in the female. The Thai program for cancer control indicates that (1) there is no effective cancer control without early diagnosis; (2) the detection of early cancer requires special effort; (3) the premise that screening programs should be directed exclusively at asymptomatic patients should be reexamined; (4) screening programs without follow-up are counterproductive; (5) screening programs will be most successful when linked with ongoing activities that represent a desired social or medical benefit; (6) totally integrated health care services offer the best opportunity for cancer control; (7) Cancer control services should be incorporated into programs offering comprehensive health care; (8) volunteer resources should be tapped to the extent that they are available; (9) environmental hazards should be eradicated; and (10) commercial marketing practices may affect cancer control. (8 Refs)

3. CANCER PATTERNS IN TRANSKEI.

Rose EF, Fellingham SA
Natl. Res. Inst. for Nutritional Diseases, South African Medical Res. Council, P.O. Box 192, East London 5200, South Africa
S Afr J Sci; 77(12):555-561 1981

During 1965-1969, 4,247 malignant tumors were diagnosed in Transkei hospitals, giving standardized rates of 60 and 40 per 100,000 per yr for males and females, respectively. The cancers were analyzed according to relative frequency, age distribution of common cancers and geographical pattern. Cancers of the esophagus, mouth, liver, uterine cervix and breast were the specific neoplasms analyzed. This study dealt with a basically rural community having little communication with urban conditions and may serve as a baseline study for comparisons of cancer patterns already established in urban communities. The pattern of cancer incidence in Transkei is changing and may be a reflection of breakdown of age old taboos and changing social conditions. Similarities were found in the geographical distribution of esophageal and oral cancer in both sexes and in females between hepatic and cervical cancer and also between cancers of the breast and esophagus. (20 Refs)

4. STUDIES OF THE MORTALITY OF A BOMB SURVIVORS. 7. MORTALITY, 1950-1978: PART I. CANCER MORTALITY.

Kato H, Schull WJ
Radiation Effects Res. Foundation, Hiroshima, Japan
Radiat Res; 90(2):395-432 1982

Mortality of survivors of the atomic bombing of the cities of Hiroshima and Nagasaki during World War II is updated to include the years 1975-1978. The excess in leukemia deaths continued to decrease during these yr from the peak in 1950-1954, and in 1975-1978 an increased mortality with dose was observed only in Hiroshima. Cancers other than leukemia have increased yearly from about 1960 and, averaged over all periods, the risk of these cancers now equals (Nagasaki) or exceeds (Hiroshima) that of leukemia. The risks of lung, breast, and stomach cancers, which were shown be significantly increased in the yr 1950-1974, have continued to rise in 1975-1978, but there has been no apparent additional increase in risk in 1975-1978 for esophageal or urinary tract cancers, which had increased previously. An elevated risk of colon cancer has become newly evident. The significant increase with dose observed for malignant lymphoma in the previous report appeared in retrospect to be spurious, stemming possibly from the inclusion of multiple myeloma. No increased risk of uterine cancer has been seen. A greater excess of a variety of tumors was observed in Hiroshima than in Nagasaki in all periods combined. The significance of the relationship between radiation and cancer is discussed. (17 Refs)

5. USE OF THE CANADIAN MORTALITY DATA BASE FOR EPIDEMIOLOGICAL FOLLOW-UP.

Smith ME, Newcombe HB
Occupational and Environmental Health Unit, Vital Statistics and Disease Registries Section, Statistics Canada, 17th Floor, R.H. Coats Building, Tunney's Pasture, Ottawa, Ontario, K1A OZ5, Canada
Can J Public Health; 73(1):39-46 1982

The Canadian Mortality Data Base (CMDB) contains all Canadian death registrations dating from 1950. The CMDB contains personal identifying information, is machine-readable and in microfiche and microfilm form, and is sequenced and consolidated to facilitate manual searching. Several follow-up studies have been performed for various 'at-risk' groups, including infant death-birth linkages, isoniazid and cancer in tuberculosis patients, a 10% sample of the Canadian labor force, and fluoroscopy and cancer in tuberculosis patients. Searches presently in progress involve nickel workers, uranium workers, Ontario workers, particularly miners, Nutrition Canada Survey participants, Ontario morticians, who have high levels of exposure to formaldehyde, railway workers, childbearing women and breast cancer, Alberta cancer files, and fluospar mining in Newfoundland. Several other searches involving the data base are under negotiation, including radiation-exposed workers. The CMDB has the potential for other searches involving individual linear follow-up to investigate health problems associated with diet, food additives, pharmaceuticals, water supply, and workplace conditions. The system is economical and need not threaten personal privacy..(46 Refs)

6. BREAST CANCER IN THE CAPITAL OF THE GERMAN DEMOCRATIC REPUBLIC, BERLIN, FROM 1975 TO 1979.

Ebeling K, Tannenberger S, Nischan P, Jarofke D, Kluge E
Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
Arch Geschwulstforsch; 52(4):307-321 1982

Statistical data on treatment and survival of patients with breast cancer (BC) in East Berlin are reviewed for the period 1975-1979. A total of 2,352 cases of BC were reported at an av yearly rate of 77.7/100,000 population. Analysis of age data indicates a steady increase in incidence of BC up to age 45 and a decline from 55 to 64 yr. During the period studied the 55-64-yr-old range accounted for a relatively constant 52% of all BC. Analysis of birth cohorts for 1887-1947 indicated a higher incidence among the younger cohorts. Berlin had a generally higher incidence than East Germany as a whole (66.7/100,000 compared with 53.8/100,000). The interval between detection of symptoms by the patient and treatment showed a decline. The fraction of cases diagnosed in Stage I and II increased from 67.7% in 1952-1959 to 71.8% in 1975-1979. Histological confirmation was obtained in 95% of case, with no significant fluctuations from yr to yr. The use of radiotherapy before or after surgery decreased from 34.2% in 1975 to 22.7% in 1979. Use of adjuvant chemotherapy increased from 4.6% to 10.5% in the same period. Radical surgery was employed in 86% of cases overall from 1975 to 1979, with a marked decline with increasing age. Survival rates for all age groups showed a continual yearly decline, reaching 67.8% at 5 yr. The 5-yr survival rate varied according to the program of treatment, being 75.8% for patients treated in cancer centers with multidisciplinary treatment and 63.5% for patients treated at other facilities. Differences were particularly marked for patients with Stage III or IV cancers. (24 Refs) (In GER)

7. GENETICS OF A FAMILIAL CANCER SYNDROME CHARACTERIZED BY SARCOMAS AND DIVERSE NEOPLASMS (MEETING ABSTRACT)

Blattner WA, Zener KA, Greene MH, Mulvihill JJ, Li FP, Fraumeni JF
National Cancer Institute, Bethesda, MD, 20205
Proc Am Soc Clin Oncol; 1:C-711 1982

In 1969, Li and Fraumeni described a familial syndrome of sarcomas (S), breast (B), and other neoplasms affecting children and young adults. The current survey of 26 families with S and one other cancer (Ca) (excluding non-melanotic skin) in first-degree relatives was undertaken to characterize the syndrome. Among 1,242 family members, 283 primary Ca's were ascertained. In 27 cases multiple primary Ca's were documented including 1 with 4 separate primaries and 3 with triple primary Ca's. Excluding the 26 S in index cases, the distribution of Ca types was: B 21%, S 12.8%, lung (Lu) 9.3%, brain (Br) 8.1%, leukemia (L) 6.6%, gastric 4.2% and pancreas 3.9%. Adrenal cortical cancers were reported in 3 children. The age distribution for certain neoplasms (S, L, Br) resembled the expected pattern, while others (B, Lu) tended to occur at a younger age than usual. Review of pedigrees revealed 2 patterns: in 12 families, Ca's clustered in distant branches traced through a single line of descent; in 10, Ca's clustered in a single sibship with multiple ancestral branches contributing to the familial tumor diathesis. Demographic characteristics and tumor types were indistinguishable in the 2 groups. These data support the concept that susceptibility mechanisms are shared by several forms of Ca including bony and soft-tissue sarcomas; brain, breast, and lung tumors; and leukemia. (1 Ref)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

8. ORAL CONTRACEPTIVE USE AND ABORTION BEFORE FIRST TERM PREGNANCY IN RELATION TO BREAST CANCER RISK.

Vessey MP, McPherson K, Yeates D, Doll R

Dept. Community Medicine and General Practice, Radcliffe Infirmary, Oxford OX2 6HE, England

Br J Cancer; 45(3):327-331 1982

A recent publication from California in this journal has suggested that both prolonged oral contraceptive use and abortion before first term pregnancy increase the risk of breast cancer in young women. Data are presented on 1,176 women aged 16-50 yr with breast cancer, interviewed in London or in Oxford, together with a like number of matched control subjects. The results are entirely reassuring, being, in fact, more compatible with protective effects than the reverse. Possible reasons for the differences between the two sets of data are discussed. (Author abstract) (8 Refs)

9. MEAT AND FAT CONSUMPTION AND CANCER MORTALITY: A STUDY OF STRICT RELIGIOUS ORDERS IN BRITAIN.

Kinlen LJ

Cancer Res. Campaign, Cancer Epidemiology Res. Group, Univ. Oxford, Radcliffe Infirmary, Oxford, England

Lancet; 1(8278):946-949 1982

The close correlations between mortality from breast and colorectal cancers and the per-caput consumption of meat or fat in different countries suggest that these dietary items may be involved in the etiology of these neoplasms. To investigate further these possible relations a study has been conducted of cancer mortality between 1911 and 1978 in two groups of enclosed religious orders for women: one of 1,769 nuns who eat no meat and one of 1,044 nuns who eat little meat. Mortality from breast and colorectal cancer was not significantly lower in either group than in the general population. It is difficult to evaluate the small reduction in breast cancer mortality in the no-meat group because of the wide confidence limits. An unexpected finding was an excess mortality from esophageal cancer in both groups. These findings concern women who reduced their meat consumption in adult life: it is suggested that they are compatible with the evidence put forward to support a role for fat or meat intake in causation of breast cancer if dietary influences in pre-adult life are important. The findings on colorectal cancer point to the etiological importance in this disease of aspects of diet other than fat or meat intake. (Author abstract) (34 Refs)

10. TRENDS IN DIET AND BREAST CANCER MORTALITY IN ENGLAND AND WALES 1928-1977.

Ingram DM
Univ. Dept. Surgery, Queen Elizabeth II Medical Center, Nelands, 6009, Western Australia
Nutr Cancer; 3(2):75-80 1981

Trends in age-adjusted breast cancer mortality and consumption of meat, fat, sugar, cereal, and fruit and vegetables were studied for England and Wales over the 50-yr period from 1928 to 1977. At the onset of World War II, there was a marked reduction in both breast cancer mortality and intake of sugar, meat and fat, and an increased consumption of cereals and vegetables. Consumption of these foodstuffs returned to pre-war levels by 1954, but breast cancer mortality did not return to pre-war levels until some 15 yr later. The association between the various dietary components and subsequent breast cancer mortality was determined for various lag intervals. Significant correlations were found for cereal, fat, sugar and meat consumption, the correlation being maximal for a diet-breast cancer death lag interval of 12 yr. These findings add weight to the hypothesis that breast cancer development is related to a diet rich in meat, fat and sugar, and that some protection against cancer may be afforded by a reduction in these dietary components and an increase in cereal consumption. (Author abstract) (20 Refs)

11. FUSARIUM MYCOTOXINS AND THE EFFECTS OF HIGH-FAT DIETS.

Schoental R
Dept. Pathology, Royal Veterinary Coll., Univ. London, Royal College St., London NW1 0TU, England
Nutr Cancer; 3(2):57-62 1981

Some of the inconsistencies encountered in epidemiological and experimental studies on the role of various types of fats in the etiology of cardiovascular disorders and certain tumors (of the breast, endometrium, and colon, among others) may be related to the presence of adventitious contaminants in the fats. Among the contaminants, mycotoxins, especially those produced in agricultural products by the Fusarium field-microfungi (the irritant trichothecenes, the estrogenic zearalenone, and other resorcylic acid lactones), warrant particular attention. Their production is favored by the wet, cool weather prevailing in areas notable for high incidences of the aforementioned disorders. The recent development of sensitive radioimmunoassays for the detection and estimation of some of these mycotoxins should facilitate the testing of the above hypothesis. (Author abstract) (39 Refs)

12. PROSPECTIVE STUDY OF A FAMILY CANCER SYNDROME.

Li FP, Fraumeni JF
NCI, Bethesda, MD, 20205
JAMA; 247(19):2692-2694 1982

Risk of cancer was studied prospectively in four families described in 1969 as having diverse neoplasms, especially breast cancer and soft-tissue sarcoma. Between 1969 and 1981, in 10 of 31 surviving family members, there developed 16 additional cancers (expected, 0.5). There were five breast carcinomas, four soft-tissue sarcomas, and seven other cancers. In eight patients, multiple primary cancers developed, including three soft-tissue sarcomas and one mesothelioma at sites of prior radiotherapy. (Author abstract) (10 Refs)

13. EPIDEMIOLOGIC CHARACTERISTICS OF MAMMARY FIBROADENOMA.

Ruiz Moreno JA, Medina Malagon LE, Alcaide Sanchez J
Departamento de Gineco-Obstetricia, Clinica de Ginecologia Oncologica, Hospital Central Militar, Mexico, D.F., Mexico
Ginecol Obstet Mex; 49(294):225-238 1981

Retrospective study (1967-1976) of patients (13-60 yr old) with mammary fibroadenoma (MFA) was analyzed and compared with 150 healthy controls. Only the patients with histologically confirmed diagnosis were included. Excluded were patients with juvenile, pregnant, lactating, and giant MFA. Of the 158 patients, only 143 had a single FAM, 2 or more MFA were found in 41, and bilateral MFA was found in 29. No relationship was observed between MFA and menstrual history, lactation, or mammary trauma. Familial history of mammary pathology, hormonal anticonceptional drugs, and nulliparity favor MFA. Ninety-six percent of the patients diagnosed themselves MFA, and went for medical consultation immediately or greater than 5 yr later. In 115 patients symptoms consisted of pain, in 18 premenstrual tension, itching of nipple in 6, and others. Without symptoms were 69 of the patients. Growth of MFA was slow in 107 of the patients, rapid in 45, and negative in 32. Size of av lesion was 3.4 x 2.9 cm and the biggest was 8 x 7 cm. Location of the MFA was in the upper outer quadrant in 110, in the lower outer in 64, in the upper inside in 30, in the lower inside in 24, and behind the nipple in 10 patients. Associated mammary pathology in 11 of the patients was fibrocystic mastopathy, in 2 each was epithelial hyperplasia, florid adenosis, fat necrosis, adenocarcinoma, and in 1 was phyllode cystosarcoma. (25 Refs) (In SPA)

14. MAMMARY CANCER: HIGH RISK FACTORS FOR ITS DEVELOPMENT.

Torres Lobaton A, Diaz Perches R, Marquez GA, Miranda Hernandez H
Unidad de Oncologia, Hospital General de Mexico, S.S.A., Mexico, DF, Mexico
Rev Med Hosp Gen Mex; 44(8):281-287 1981

High risk factors in development of mammary cancer (MC) were discussed, and the following aspects were included: age, height, wt, heredity, dietary factors, personal history of MC, benign mammary pathology, exposure to ionizing irradiation, menstruation, menopause, parity, and hormones. Intake of estrogens under any form especially after menopause was also considered. (50 Refs) (In SPA)

15. PROSTAGLANDINS AND BENIGN MASTOPATHIES.

Rolland PH, Martin PM, Bourry M, Serment H
Laboratoires des recepteurs hormonaux de Cancerologie Experimentale, Faculte de Medecine de Marseille (Secteur Nord), F 13326 Marseille Cedex 3, France
J Gynecol Obstet Biol Reprod (Paris); 10(3):197-201 1981

Levels of plasma estrogen (E), progesterone (P), and prostaglandin synthetase (PS) activity were measured in 22 women (23-28 yr old) who had symptoms of benign mastopathy or mastodynia during all or part of their menstrual cycle. Thermographic examinations were performed. In general, E and P levels were decreased in the patients as compared with normal subjects. Prostaglandin E2 (PGE2) levels were increased during both phases of the menstrual cycle among patients. In four benign lesions examined, levels of PS activity were variable. Patients with low estrogen levels showed a pronounced thermographic response to treatment with prostaglandin inhibitors, while patients with high relative estrogen levels showed no such response. The relationships between E, P, and PGE2 levels and risk of breast cancer are discussed. (19 Refs) (In FRE)

16. RESEARCH ON THE MENOPAUSE.

WHO Scientific Group on Research on the Menopause, Bancroft J, Burger HG, Devi PK, Mack TM, Nordin BE, Nylander P, Ryan KJ, Sas M, Sinnathuray TA
World Health Organization, Geneva, Switzerland
WHO Tech Rep Ser (670): 120 pp., 1981.

The controversy over the existence of a menopausal syndrome of somatic and psychological symptoms and illness and the lack of data on the age distribution of menopause (MP) and on menopausal sociocultural significance in developing countries are discussed. The endocrinology of MP, age distribution, sociocultural significance of MP in different settings, symptoms associated with MP, disorders resulting from or possibly accelerated by MP, risks of therapeutic estrogens and progestins to peri- and postmenopausal women with particular reference to neoplasia, fertility-regulating methods for women approaching MP, and estrogens and the health care management of peri- and postmenopausal women are reported. Summaries of three studies of endometrial carcinoma conducted before 1975 and of case-control studies of endometrial cancer (EC) with epidemiological details are presented. Two major areas of ignorance in regard to risks of EC associated with estrogen therapy are the persistence of the oncogenic effect, and the nature of the dose-response curve at low doses and duration of use. Epidemiology of breast cancer (BC) is even more suggestive of endocrine origins than that of EC. Risk is related to a variety of endocrine phenomena, including ages at menarche, MP, and first pregnancy. Early oophorectomy has long been recognized to be strongly protective. Cohort studies and case-control studies of estrogen therapy and BC are presented. Several mechanisms for the relationship between endogenous hormones and BC have been proposed. Both naturally occurring and synthetic estrogens and progestins appear under some circumstances to be carcinogenic for BC in animal species. (383 Refs)

17. RELATIONSHIP OF AGE AND STRAIN TO MAMMARY GLAND DNA DAMAGE, REPAIR AND REPLICATION IN VIVO (MEETING ABSTRACT)

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Fed Proc; 41(3):1559 1982

The incidence of mammary gland carcinogenesis depends strongly upon the age and strain of animal. In order to elucidate the underlying mechanisms responsible for these observations, we quantitated: a) the initial levels of alkali sensitive sites induced from a single dose of ENU (ethylnitrosourea) with the use of alkaline sucrose gradient sedimentation in rats both susceptible (Sprague Dawley [SD]) and resistant (Long Evans [LE]) to mammary gland carcinogenesis; b) the fate of such damage in female SD and LE rats at both 30 and 50 days of age; c) the degree of normal gland proliferation in both age groups; and d) the short term effect of ENU on normal mammary gland proliferation. An index of mammary gland proliferation was determined by incorporation of [3H]thymidine into mammary DNA over a two hour time period. Our data showed: a) the initial level of damage induced was higher in the 50 day than the 30 day old rat; b) the alkali labile sites appeared to decrease in both age groups, over the seven day period studied; c) loss of alkali labile sites appeared to be faster in the LE than in the SD rats; and d) normal mammary gland proliferation decreased after a single treatment with ENU. These data relate the induction and persistence of DNA damage (single strand breaks and alkali labile sites) in vivo to mammary gland carcinogenesis as a function of age and strain of rat. (no Refs)

18. SEPARATION OF HIGH MAMMARY TUMOR INCIDENCE FROM HIGH HEPATOMA INCIDENCE IN BACKCROSS MICE DURING SEGREGATION OF THE VIABLE YELLOW GENE.

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Int J Cancer; 29(5):587-590 1982

Mammary tumorigenesis in strain C3H/AvyfB female mice (approx 90% incidence) is not due to exogenous mouse mammary tumor virus (MMTV) but to genetic factors transmitted by either parent. Prominent among these genetic factors is the viable yellow (Avy) gene which may increase either the virulence of the endogenous MMTV provirus (Mtv-1) by promoting expression of the susceptibility of the mammary tissue to tumorigenesis by endogenous MMTV. Unexpectedly, the F1 hybrid females (AvyA) developed mammary tumors at a relatively low rate although hepatoma incidence remained high. Both yellow (AvyA) and agouti (AA) backcross females showed an even greater reduction in mammary tumor incidence, 7.9% and 3.8% respectively. In contrast, the high rate of spontaneous hepatoma development segregated with the Avy gene since 86-5% of the yellow (AvyA) backcross females development hepatomas by 19 mo of age, while only 25% of the agouti (AA) backcross females had liver tumors at 24.4 mo. The reduction of mammary tumor incidence in (C3H-AvyfB x C3H/Sm)F1 hybrids was unexpected since earlier studies had shown that reciprocal F1 hybrids between strains BALB/c and C3H-AvyfB continued to show a 90% mammary tumor incidence. The present result is consistent with the possibility that strain C3H/Sm possesses a heritable factor(s) which attenuates the ability of endogenous MMTV to malignantly transform mammary epithelium. (15 Refs)

POSSIBLE IATROGENIC FACTORS IN HUMAN BREAST CARCINOGENESIS

19. SECOND MALIGNANCIES IN OPERABLE BREAST CANCER (MEETING ABSTRACT)

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Proc Am Soc Clin Oncol; 1:C-324 1982

Second malignancies (SM) represent one of the potential hazards of modern cancer treatment, especially radio- and chemotherapy after surgery for breast cancer. For this reason, regional cancer registry data (1960-75) on 1985 breast cancer patients (pts) were analyzed for SM in the retrospective part of our study. SM were observed in 77 cases (4%), of which 17% were found before, 18% simultaneously and 65% after the diagnosis of breast cancer. Most frequent SM were of GI-(35%), GYN-(22%), breast (13%) and CNS-origin (10%). No difference in the rate of SM was found between the major treatment groups: The median time from mastectomy to diagnosis of SM was 3 years. Sixty-six percent of SM were observed within 5 and 89% within 10 years. Median survival of pts with SM diagnosed post mastectomy was 4.8 years from primary breast surgery while it was only 4 months in pts with a SM observed before and 12 months in those with a SM diagnosed simultaneously with breast cancer. These data were confronted with the prospective part of the study, where 5/123 (4.1%) of pts in the surgical control regimen and only 1/118 pts (0.8%) with adjuvant LMF (Chlorambucil, Methotrexate, 5-Fluorouracil) + BCG developed SM within 6 years median observation time post mastectomy. These data are compared to other current adjuvant breast trials and do not indicate an increased risk of SM by present adjuvant therapy. (no Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

20. CARCINOGENICITY OF 2-AMINO-4-(5-NITRO-2-FURYL)THIAZOLE IN RATS BY ORAL AND SUBCUTANEOUS ADMINISTRATION.

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Carcinogenesis; 3(3):275-277 1982

Female Fischer rats were divided into two groups and fed either basal diet or basal diet containing 0.166% 2-amino-4-(5-nitro-2-furyl)thiazole for 52 wk followed by basal diet for an additional 16 wk. Out of the 24 rats fed 2-amino-4-(5-nitro-2-furyl)thiazole, 23 had forestomach tumors, 4 had fibroadenomas and 2 had adenocarcinomas in the mammary glands, 2 had renal pelvic carcinomas, 5 had papillomas and 6 had carcinomas in the bladder, and 2 had cutaneous tumors. None of the 10 rats fed basal diet developed tumors. In another study, 2-wk-old Fischer rats of both sexes were injected sc once a wk for the first 8 wk with 2-amino-4-(5-nitro-2-furyl)thiazole at a dose of 10 mg/kg and then 1.4 mg/rat for an additional 46 wk. The control rats were injected with solvent (dimethyl sulfoxide:water, 1:1) only. The experiment was terminated at the end of 58 wk. Malignant fibrous histiocytomas were found in 5 out of 8 male rats and 4 out of 11 female rats, and and angiosarcoma was found in one out of eight male rats injected with 2-amino-4-(5-nitro-2-furyl)thiazole. None of the control rats developed tumors. (Author abstract) (12 Refs)

21. TRANSPLANTATION OF MOUSE MAMMARY EPITHELIAL CELLS GROWN IN PRIMARY COLLAGEN GEL CULTURES.

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Cancer Res; 42(6):2376-2383 1982

A technique for the transplantation of mouse mammary epithelial cells, grown in collagen gels, has been developed that demonstrates that the phenotype of the cells prior to culture was not altered by the culture conditions. Mammary epithelial cells from virgin and midpregnant C57BL/Crgl mice; virgin, midpregnant, and multiparous nonpregnant BALB/cfC3H/Crgl mice; a BALB/c hyperplastic alveolar nodule line, and mammary tumors from BALB/cfC3H/Crgl mice were embedded inside collagen gels and grown for 10 to 14 days in the presence of 25% swine serum plus cholera toxin (0.01 ug/ml). The epithelial cells increased in number during the culture period. At the end of the culture period, the cells were removed from the collagen gels and transplanted to the gland-free mammary fat pads of 3-wk-old syngeneic female mice. Culture in collagen gels increased the number of cells necessary to obtain a high percentage of mammary outgrowths as compared to cells not grown inside collagen gels. In general, mammary cells grown inside collagen gels gave rise to outgrowths, similar in phenotype to those from noncultured cells, and were representative of the tissue of origin. Mammary epithelial cells from C57BL/Crgl virgin donors grown in collagen gels for 10 to 14 days retained their ability to respond to the endogenous hormones of pregnancy and lactation of the host and formed lobuloalveolar structures full of secretion similar to the host's own mammary gland. The data indicate that the growth of mammary epithelial cells in collagen gels and subsequent transplantation into the gland-free fat pads of syngeneic hosts provides a simple system, wherein cells can be grown in vitro and their phenotypes determined in vivo. (Author abstract) (27 Refs)

22. SURVIVAL OF MOUSE MAMMARY GLAND TRANSPLANTS OF NORMAL, HYPERPLASTIC, AND TUMOR TISSUES EXPOSED TO X-RAYS.

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JNCI; 68(4):613-618 1982

Mouse mammary tissues, including ducts, prelactating lobules, hyperplastic outgrowth lines, and tumors, were exposed to varying doses of x-rays and then transplanted to fat pads of nonirradiated BALB/c mice for study. Estimates of the dose of radiation that would allow survival of 50% of the transplants (SD50) were made with the use of probit analysis. Nearly all duct and lobule transplants survived doses of x-rays from 0 to 800 rad. The survival rate declined rapidly following doses above 800 rad, and the calculated SD50 was 1,020 and 1,260 rad for mammary ducts and lobules, respectively. The three hyperplastic outgrowth lines tested gave very different results. Hyperplastic line Z5C1 transplants had better than 90% survival at doses up to 1,200 rad and an SD50 between 1,200 and 1,600 rad. Hyperplastic line Z5D transplants had an SD50 of between 800 and 1,200 rad. Hyperplastic line D1 transplants had a better than 90% survival following doses of 0-600 rad and an SD50 between 600 and 800 rad. The survival of tumor transplants was 100% following doses of x-rays up to 1,200 rad; the SD50 was in excess of 1,600 rad. The mouse mammary transplantation system can be used to study the direct effect of x-rays on normal, premalignant, and malignant mammary tissues and provides a basis for the study of the radiobiology of mammary tissues. (Author abstract) (14 Refs)

23. CARCINOGENICITY AND TOXICITY OF 1,2-DIBROMOETHANE IN THE RAT.

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Toxicol Appl Pharmacol; 63(2):155-165 1982

The chronic effects of 1,2-dibromoethane (ethylene dibromide, EDB) were investigated in rats. Three experimental groups were studied: (1) inhalation of 20 ppm EDB over an 18-mo period, (2) 0.05% disulfiram (DS) in the diet for 18 mo, and (3) combined treatment of 20 ppm EDB + 0.05% DS. Rats receiving DS only showed less body wt gain than controls or EDB-exposed rats over the 18-mo period. Rats receiving EDB + DS had lower wt gain than animals receiving either EDB or DS alone. A correlation between low food consumption and low body wt gain was found in rats treated with

DS or DS + EDB. EDB-treated or EDB + DS-treated rats exhibited high mortality compared with control rats or those treated with DS alone. While hematological findings were normal for EDB-treated rats, EDB + DB treatment resulted in low hematocrit, hemoglobin, and red blood cell counts. Male rats treated with DS alone did not exhibit any significant histopathological changes except for a higher incidence of hemosiderosis of the spleen; females had a higher incidence of mammary tumors and of hemosiderosis of the spleen. Rats inhaling EDB alone had a higher incidence of tumors, in one or both sexes, in the spleen, adrenal, subcutaneous mesenchymal tissue, and mammary gland compared to controls. Combined treatment with EDB + DS caused an increased incidence of tumors in one or both sexes, in the liver, kidneys, thyroid, lungs, and spleen compared to treatment with either EDB or DS alone. Combined treatment also caused a higher incidence of atrophy of the testes and spleen compared to treatment with EDB alone. These results indicate that DS, a drug used in the treatment of chronic alcoholism, enhances the toxicity and carcinogenicity of EDB. Such an effect may be significant in evaluating the hazards of industrial exposure to EDB in workers who are being treated in alcohol control programs. (37 Refs)

24. TUMOR DEVELOPMENT IN X-IRRADIATED TRANSPLANTS OF NORMAL AND HYPERPLASTIC MOUSE MAMMARY GLANDS (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:921 1982

The risk of increasing tumor development following exposure of the mammary gland to x-rays is being investigated using the inbred BALB/c mouse and several serially passaged lines of hyperplastic mammary tissue. To avoid the complications of whole body exposure, the mammary tissue was transplanted to non-irradiated hosts. The donor tissue was exposed to whole body x-irradiation of 0, 25, 75, 225 and 675 RAD. Within an hour 0.5mm cubes of tissue were excised and transplanted to host gland free inguined fat pads. The 60 to 100 transplants in each dose group were observed weekly for tumor development. Transplants of mammary ducts have been in the host mice for over one year and no tumors have been observed in any of the dose groups. The hyperplastic outgrowth line Z5C1, has shown a response in the cummulative tumor incidence curves that is proportional to dose. The slope of the incidence curves for 0, 25, and 75 RAD are not different. However, the latency period is decreased 4 and 5 weeks for the 25 and 75 RAD groups, respectively. In the 225 and 675 dose groups the latency period is increased, however, the slope of the incidence line is much steeper and reaches the 50% incidence level before the lower doses or controls. Studies with other hyperplastic outgrowth lines are in progress and preliminary data suggests a variable response for each outgrowth line depending on its normal tumor incidence rate. (no Refs)

25. INDUCTION OF MAMMARY TUMORS IN VIRGIN FEMALE BALB/C MICE BY SINGLE LOW DOSES OF 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:905 1982

These experiments were initiated to examine the relationship between low doses of DMBA and the induction of mammary tumors in virgin female BALB/c mice. Twelve-week-old mice were exposed to single or multiple doses of DMBA ranging from 0.0025 mg to 12.0 mg by gastric intubation. Mice were checked regularly for mammary tumors and the experiment was terminated when the mice were 800 days of age. In the dose range of 0.0025 mg to 0.125 mg of DMBA the incidence of mammary tumors was directly proportional to dose. At doses above 0.125 mg the dose response curve began to bend over and above 0.5 mg the mammary tumor incidence was independent of dose. In the low dose region administration of DMBA as multiple exposures did not affect the tumor response. Analysis of the data for the incidence of mammary tumors with time after DMBA administration suggested that carcinogen exposure both accelerated the appearance of otherwise 'spontaneous' neoplasms as well as induced new mammary tumors. Further, the predominant effect of increasing the dose of DMBA was to shorten the time of onset of these tumors without changing their rate of appearance. Finally, carcinogen dose affected the histological type of tumors observed. Greater than 90% of the mammary tumors induced by DMBA doses which were on the ascending portion of the dose response curve were adenocarcinomas. At doses which were on the plateau of the dose response curve, increasing the dose served only to increase the relative proportion of adenoacanthomas to adenocarcinomas. (no Refs)

26. MODELS OF HUMAN BREAST CANCER.

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Breast Cancer Management: The Experience of the Combined Breast Clinic, St. George's Hospital/The Royal Marsden Hospital. Coombes RC, Powles TJ, Ford HT, and Gazet JC, ed. London, Academic Press, 317 pp., 1981.

The canine, rodent, and human models of breast cancer and results of recent studies are discussed. Eight serially transplantable lines of human breast cancer xenografts have been established in immune-suppressed mice. These lines have resulted from implantation of 102 different specimens of primary and secondary breast carcinoma into approx 1,000 mice. The main uses for such xenografts are preclinical assessment of drugs thought to be of potential value against breast cancer and in the field of experimental pathology. (15 Refs)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

27. TOXICOLOGY, CARCINOGENICITY, AND TERATOGENICITY OF SOME ORALLY ADMINISTERED RETINOIDS.

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J Am Acad Dermatol; 6(4,part2):652-659 1982

The acute toxicities of vitamin A (VA), all-trans-retinoic acid (t-RA: tretinoin), 13-cis-retinoic acid (c-RA: isotretinoin), and etretinate (Ro 10-9359) are relatively low in rats, mice, and rabbits. Subchronic toxicity studies in rats, mice, and dogs suggest that t-RA is somewhat more toxic than c-RA. chronic toxicity studies indicate a marked intolerance of dogs to chronic high-dose treatment with Ro 10-9359. Rats are less tolerant to Ro 10-9359 than to c-RA. In Ames assays, the retinoids are nonmutagenic, except for a weakly positive reaction in strain TA-100 at a high concentration of Ro 10-9359. The carcinogenicity of c-RA (2-32 mg/kg/day x 105 wk) was studied in Fischer 344 rats. Animals given the highest doses, and females given intermediate doses, showed a higher frequency of pheochromocytomas than the controls. The significance of this finding is not clear, in view of the high frequency of spontaneous pheochromocytomas in this strain. All males given c-RA showed fewer adenomas or angiomas of the liver than the male controls. The carcinogenicity of Ro 10-9359 (0.5-3.0 mg/kg/day x 104 wk) was studied in OFA:SPF rats. Rats given the two highest doses (1-3 mg/kg) showed a lower frequency of multiple tumors, and females given the highest dose showed a lower frequency of mammary tumors than the controls. No increase in the frequency of any neoplasm was observed at any dose. In rats and rabbits, c-RA caused fewer adverse effects on reproductive performance or fertility, fewer fetal abnormalities, and fewer adverse effects on postnatal development than VA, t-RA, or Ro 10-9359. (24 Refs)

28. INHIBITION OF CHEMICAL CARCINOGENESIS BY RETINOIDS.

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J Am Acad Dermatol; 6(4,part2):809-814 1982

Experiments involving two-stage skin carcinogenesis in mice, the induction of bladder tumors in rats or mice by N-methyl-N-nitrosourea (MNU) or N-butyl-N-(4-hydroxybutyl)nitrosamine (OH-BBN), the induction of mammary tumors in rats by MNU, and the induction of esophageal tumors in rats by N-methyl-N-benzylnitrosamine have demonstrated several important structure-activity relationships in the inhibition of chemical carcinogenesis by retinoids. The aromatic ring, side chain, and polar terminal groups of the retinoid molecule have important effects on the agent's organ distribution and thus its anticarcinogenic activity. Retinoids that significantly inhibit OH-BBN bladder carcinogenesis include 13-cis-retinoic acid (c-RA), ethyl retinamide, 13-cis-ethyl retinamide, 2-hydroxyethyl retinamide, 4-hydroxyphenyl retinamide (4-HPR), 13-cis-4-hydroxyphenyl retinamide, and 2-hydroxypropyl retinamide. Retinoic acid (RA) is a less favorable preventer of MNU-induced mammary tumors in rats than 4-HPR, because 4-HPR accumulates to a lesser extent in the liver and so is less hepatotoxic than RA. Synergistic interactions between retinoids (eg, RA or 4-HPR) and hormonal treatments in MNU mammary carcinogenesis have been discovered. Retinoid treatment from the time of carcinogen administration or the first excision of a carcinogen-induced tumor has greater chemopreventive activity than delayed treatment. The efficacy of delayed retinoid treatment largely depends on the tumor's latent period. The authors' current research involves the identification of new retinoids having lower toxicity and higher chemopreventive activity, combination treatments having synergistic antitumor activity, and the mechanisms of action of the retinoids. (28 Refs)

29. CURRENT VIEWS ON THE NATURE OF MYOEPITHELIAL CELLS AND THEIR ROLE IN THE MORPHOGENESIS OF DYSHORMONAL HYPERPLASIAS AND BREAST TUMORS.

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Arkh Patol; 44(2):69-73 1982

Literature data on the histogenesis of myoepithelial cells and their role in the etiology of breast dysplasias and breast neoplasms are reviewed. Analysis of normal cytogenesis and differentiation in myoepithelium showed that myoepithelial cells originate from nondifferentiated clear cells. The type of distribution of myoepithelial cells can be used as a marker of early stages of invasive breast carcinoma. (50 Refs) (In RUS)

30. ROLE OF NATURAL PROSTAGLANDINS IN THE CONTROL OF MURINE MAMMARY TUMOR VIRUS EXPRESSION.

Svec J, Svec P, Halcak L, Thurzo V
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J Cancer Res Clin Oncol; 103(1):55-67 1982

The regulation of murine mammary tumor virus (MuMTV) production by mammotropic hormones, hormonomimetic substances, and cyclic nucleotides was investigated. The virus produced in control and treated mammary tumor cell cultures was quantitated by measuring the supernatant reverse transcriptase activity in exogenous reaction using poly(rC).oligo(dG) as template-primer. Two days after exposure, the synthetic glucocorticoid, dexamethasone (DXMT), increased spontaneous MuMTV production at optimal concentration (0.1 umol) up to 10x. Dibutyryl derivative of cyclic AMP had no effect on spontaneous MuMTV production, whereas the drug potentiated suboptimal concentrations of the glucocorticoid. Natural prostaglandins, potent agonists of adenylate cyclase catalyzing intracellular synthesis of cyclic AMP, enhanced both basal (up to 5x) and DXMT-stimulated (up to 1.6 times) MuMTV replication. The MuMTV-stimulating activity of prostaglandins decreased in the order of PGA1 greater than PGE1 greater than PGB1 greater than PGF2 alpha. Prostaglandins can be replaced partially by norepinephrine and isoproterenol by enhancing the DXMT-mediated MuMTV stimulation, whereas these drugs remained without effect on spontaneous MuMTV production. Theophylline, an antagonist of cAMP-phosphodiesterase converting cAMP to AMP, enhanced the virus-stimulating activity of DXMT as well as of prostaglandins. The enhancement of MuMTV production by adenylate cyclase agonists do not correlate absolutely with the estimates of intracellular cAMP levels, since the highest amounts of cAMP have been repeatedly observed in cells treated with PGE1 and norepinephrine. The results indicate that besides hormones, other hormone-like substances and cyclic nucleotides may be involved in the complex mechanism of hormone-regulated MuMTV genome expression. (Author abstract) (55 Refs)

31. MODULATION OF 5-FU METABOLISM IN HUMAN MCF-7 BREAST CARCINOMA CELLS.

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Cancer Chemother Pharmacol; 8(1):87-91 1982

A previously reported relationship between the incorporation of 5-fluorouracil (5-FU) into total cellular RNA and loss of clonogenic survival in the human MCF-7 breast carcinoma cell line was studied in cells exposed to 5-FU and modulating agents such as N-(phosphonacetyl)-L-aspartate (PALA), methotrexate (MTX), and 6-methylmercaptopurine riboside (MMPR). Cells were grown in log phase and PALA (0.01, 0.10, and 1.0 mg/ml) and MTX or MMPR (concentrations of 10(-5)-10(-7) M) were added. Incorporation of 3H-FU and 32P into MCF-7 nucleic acids was measured, intracellular phosphoribosylpyrophosphate (PRPP) was determined, and clonogenic survival of MCF-7 cells was examined. Intracellular levels of PRPP were increased in the cells with the addition of PALA, MTX, and MMPR, while little if any significant increase in the absolute amount of FU incorporated into RNA was observed. The combination of PALA/MMPR resulted in the greatest absolute increases in formation of (5-FU)RNA (almost 2x control values). However, since PALA, MTX, and MMPR inhibit RNA synthesis, the absolute amount of 5-FU incorporated would not reflect the frequency of 5-FU substitution for uracil. In the presence of the modulating agents, the [3H]FU/32P ratio correlated better with loss of MCF-7 clonogenic survival than did the absolute amount of 5-FU incorporated in RNA. The [3H]FU/32P ratio may be useful for monitoring effects of other modulating agents on the metabolism of 5-FU. The relationship between (5-FU)RNA formation and loss of clonogenic survival should be corrected for the amount of newly synthesized RNA when 5-FU is combined with modulating agents that alter rates of RNA synthesis. (12 Refs)

32. INHIBITION OF DIMETHYLBENZANTHRACENE-INDUCED TUMORS IN RATS BY STRESS (MEETING ABSTRACT)

Goldman PR, Vogel WH
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Fed Proc; 41(3):1559 1982

Previous reports have indicated that various types of physical and psychological stressors inhibit the growth of 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumors in Sprague-Dawley (S-D) rats. Dopamine (DA)-stimulated adenylate cyclase activity in the caudate nucleus has been claimed to be inversely associated with spontaneous mammary tumors in mice. We tried to replicate some of these findings and investigate some factors likely to be involved in this inhibition. Female S-D rats were used for induction of tumors by DMBA. Rats subjected to daily sessions of immobilization 5 days a week for 9 weeks showed a significant decrease in tumor weight when compared with non-stressed rats; 2.7g vs 5.4g per rat, N-20. Housing animals individually significantly increased the size of tumor over group-housed animals, 13.9g vs 5.0g per rat, N-20. However, rats bred for high versus low plasma catecholamine levels in response to stress did not differ in the weight of their tumors. No difference was seen in the number of tumors in any of these groups. Behavioral testing of emotionality prior to DMBA exposure showed no correlation to later tumor formation. DA-stimulated adenylate cyclase activity was found to be lower in animals which are more susceptible to tumor induction, 107 vs 142%, N-11. Short term immobilization stress had no effect on this DA stimulated adenylate cyclase activity. (no Refs)

33. INFLUENCE OF INHIBITORS OF PLANT CELL DIVISION AND WALL FORMATION ON MAMMARY TUMOR CELLS IN PRIMARY CULTURE (MEETING ABSTRACT)

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Department of Anatomy, Regional Cancer Center University of Louisville, Louisville, KY, 40292
Fed Proc; 41(3):1313 1982

The inhibitory effect of coumarin (1,2-benzopyrone) and 2,6-dichlorobenzonitrile (DBN) on division and wall formation in plant cells has been demonstrated. The two agents effect the cells differently; while coumarin stops nuclear division, DBN inhibits cytokynesis. In testing effects of these compounds on mammalian cells, we have used 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumors maintained as monolayer primary cultures. Cells were treated with 10(-3)-10(-9) coumarin or DBN for 24 hours. At concentrations of 10(-9)-10(-8) M cytotoxic or ultrastructural changes were not apparent but at 10(-3)-10(-5) M adverse effects became evident. At 10(-3) M coumarin destroyed the entire culture and at 10(-4) M only 50% of cells survived. At 10(-4) M DBN 80% of cells survived. Autoradiographic data showed that 10(-4) M coumarin totally arrests DNA synthesis. The same concentration of DBN was entirely ineffective. Ultrastructurally the cells surviving coumarin treatment exhibited abnormal chromatin aggregation and vesiculation of RER (rough endoplasmic reticulum). Cells treated with DBN showed fewer subcellular change but revealed increase mitochondrial density and some dilation of RER. These findings are consistant with those reported in plant cells and provide a foundation for more extensive studies of the action of these agents on mammalian tumor cells. (no Refs)

34. BIPHASIC INFLUENCE OF SELENIUM ON CELL GROWTH AND THE SYNTHESIS OF COLLAGEN IN CULTURED MAMMARY TUMOR CELLS (MEETING ABSTRACT)

Lewko WM, McConnell KP
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Fed Proc; 41(3):623 1982

Selenium is an esstential trace element which has antineoplastic properties. The effects of selenium on cell growth and macromolecular synthesis were analyzed using primary cultures of tumor cells. These cells were prepared from mammary tumors induced in rats by N-nitrosomethylurea. The growth of these tumors has been shown to be dependent upon the synthesis of type IV collagen, the only collagen detectable in cultures of these cells. Other evidence indicated that sodium selenite became incorporated into the collagen of rat skin. The effect of selenium on collagen synthesis was measured by the incorporation of 3H-proline into collagenase-sensitive protein. Lower concentrations of sodium selenite (0.001-0.1ug/ml medium) modestly stimulated cell growth, the incorporation of 3H-thymidine into DNA and the synthesis of type IV collagen. Higher concentrations of sodium selenite (10-100 ug/ml) depressed cell growth, the synthesis of DNA and decreased the synthesis of collagen over that of non-collagen protein. These results suggested that a decrease in collager synthesis could be responsible for the decreased cell growth and the anti-neoplastic effects of selenium observed in these tumor cells. (no Refs)

35. DIFFERENTIAL EFFECTS OF DIETARY ANTIOXIDANTS OF CHEMICAL CARCINOGENESIS (MEETING ABSTRACT)

King MM, McCay PB
Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104
Fed Proc; 41(3):358 1982

Female weanling Sprague-Dawley rats were fed a defined semipurified diet with antioxidants being supplemented throughout the experiments as indicated. In one set of experiments, the diets were supplemented with butylated hydroxytoluene (BHT). The rats were given a 10 mg oral dose of 7,12-dimethylbenz(a)anthracene at 50 days of age. The incidence of mammary adenocarcinomas was markedly lower in the BHT-supplemented rats compared to rats fed the same diet without BHT. When butylated hydroxyanisole (BHA) was supplemented in the diet instead of BHT, no inhibition of mammary tumor development was observed. In similar experiments, it was found that propyl gallate supplementation also offers protection against DMBA-induced tumorigenesis while alpha-tocopherol does not. These results raise the question: is the antioxidant property of the supplement actually related to inhibition of tumorigenesis or is it some other property of particular antioxidants (in this case, BHT and propyl gallate)? To determine if BHT may possibly be affecting some metabolic system associated with the activation of DMBA to the ultimate carcinogen, the effect of BHT supplementation on tumor induction was compared between a direct acting mammary carcinogen (nitrosomethylurea) and DMBA, which does require metabolic activation. BHT inhibited DMBA- but not NMU-induced mammary tumorigenesis, suggesting that the influence of BHT may involve inhibition of DMBA activation. (no Refs)

36. EFFECTS OF DIETARY PROTEIN ON RELEASE OF OVARIAN STEROIDS AND DEVELOPMENT OF DMBA-INDUCED BREAST TUMORS IN RATS (MEETING ABSTRACT)

Huang HH, Kissane JQ, Drab E, Hawrylewicz EJ
Department of Research, Mercy Hospital and Medical Center, Chicago, IL, 60616
Fed Proc; 41(3):280 1982

Virgin rats were fed 8%, 19.5% or 31% isocaloric protein diets for a period of 3 weeks before mating. The diets were maintained throughout the mating, gestation and lactation periods. After weaning, all pups were continued on their respective diets and ate ad libitum during the entire experimental period. DMBA (dimethylbenzanthracene) was administered intragastrically at dose of 3mg/100 g BW at the age of 3 weeks after vaginal opening. Serum estradiol and progesterone were measured at the time of DMBA administration and 6 months after DMBA treatment. Six months after DMBA 30% in 8%, 48% in 19.5%, and 73% in 31% protein diet rats exhibited breast tumors. Estradiol was significantly less in 8% protein group at 3 weeks after vaginal opening, as compared to the same stages of estrous cycle of 19.5% or 31% protein group; progesterone was significantly lower in 8% protein group at diestrous and proestrous afternoon as compared to those of high protein groups. There was no difference in estradiol and progesterone among these 3 groups of rats at 6 months after DMBA treatment. These data indicate that the lower incidence of DMBA-induced breast tumors in lower protein diets rats may be partly due to the low ovarian hormone profile at the time of DMBA exposure. (no Refs)

37. UPTAKE AND LOCALIZATION OF SELENIUM IN MAMMARY EPITHELIAL CELL LINES (MEETING ABSTRACT)

Medina D, Lane H
Baylor College of Medicine, Houston, TX, 77030
Proc Am Assoc Cancer Res; 23:902 1982

Previous experiments demonstrated that selenium supplementation inhibited both viral-and chemical carcinogen-induced mouse mammary tumorigenesis. In order to understand the basis for selenium-mediated inhibition of mammary tumorigenesis, the uptake and localization of selenium was examined in 3 mammary epithelial cell lines (CL-S1, YN-4 and WAZ-2t), which exhibited different sensitivities to selenium-modulation of cell growth. All three cell lines incorporated 75Se over 24-48 hrs, although the maximum amount incorporated was on the order WAZ-2t, YN-4, CL-S1. Glutathione peroxidase, a selenoenzyme, was present in all 3 cell lines with the same relative order. Labeled selenium localized primarily in the cytosol compartment (59%) and secondarily, in the mitochondrial compartment (21-23%). The half-life of labeled selenium in the cells was 2.6 days. After a cold-chase wash, the labeled selenium turned over to the same extent in the cytosol and mitochondrial compartments. The three cell lines were exposed to 5 x 10-8M, 5 x 10-6M, and 5 x 10-5M selenium and processed for examination by transmission electron microscopy. No effects on cellular organelles and general cellular architecture were seen at 5 x 10-8M selenium. At 5 x 10-6M selenium, YN-4 exhibited a marked electron-dense deposit in virtually all of the mitochondria of the cells. Mitochondria of the cell lines CL-S1 and WAZ-2t were unaffected at this dose. (no Refs)

38. EFFECT OF THYMOSTIMULIN ON ACTIVITY OF CERTAIN ENZYMES OF ADENOSINE AND AMP METABOLISM IN RAT LYMPHOCYTES DURING MAMMARY GLAND CARCINOGENESIS.

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Res. Roentgenoradiological and Oncological Inst., Kiev, USSR
Ukr Biokhim Zh; 54(2):154-158 1982

The effect of thymostimulin (TS) on metabolism of adenosine and AMP was studied in random-bred female rats with dimethylbenz(a)anthracene induced mammary gland tumors. Animals received nine injections of TS with 10-day interval between the injections; total dose of TS was 9 mg/rat. In thymus lymphocytes of intact rats, TS produced a 1.3x increase of adenosine deaminase (ADA) activity, 1.6x decrease of 5'-nucleotidase activity, and 1.4x decrease of AMP-aminohydrolase (AH) activity. In spleen lymphocytes, TS administration resulted in a 1.5x decrease of adenylate kinase (AK) activity. The latent period of mammary gland carcinogenesis was characterized by the decrease of ADA, AK, and 5'-nucleotidase activities on day 10 followed by an increase of the activities of the enzymes tested on day 30. TS administration during the latent period of mammary gland carcinogenesis resulted in the decrease of all enzymes tested. These findings indicate that administration of thymosin-like substances can stimulate the functional activity of immunocompetent cells in animals with precancerous conditions. (17 Refs) (In RUS)

39. THE EFFECT OF OVARIECTOMY ON EXCRETION OF URINARY STEROIDS AND TUMOR GROWTH IN RATS BEARING 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED MAMMARY CANCER.

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Gan; 73(2):234-238 1982

The relation between the excretion of urinary steroids and the therapeutic effect of ovariectomy on tumors was investigated in female Sprague-Dawley rats bearing 7,12-dimethylbenz[a]anthracene-induced mammary cancer. Ovariectomy significantly reduced the excretion of urinary androgen, 11-deoxy-17-oxosteroid (11-DOOS), but hardly affected that of urinary corticosteroid, 17-deoxy-corticosteroid (17-DOCS). The responsiveness of tumors to ovariectomy was positively correlated with both pre-operative 11-DOOS and pre-operative ratio of 11-DOOS to 17-DOCS, and negatively correlated with pre-operative 17-DOCS. The extent of tumor regression after ovariectomy was associated with the decrease of urinary androgen. A similar correlation was observed between the decrease in the ratio 11-DOOS/17-DOCS and tumor suppression during cyclophosphamide treatment (medical ovariectomy). These results indicated that the tumor response to ovariectomy was related to a shift of the endogenous hormone balance from a relative dominance of androgen to relative dominance of corticosteroid. The significance of the hormonal findings is discussed in the light of the steroid metabolism in human breast cancer. (Author abstract) (16 Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

40. ECTOPIC HUMAN CHORIONIC GONADOTROPIN PRODUCTION IN DIFFERENT FORMS OF MALIGNANCY.

Das S, Bhattacharyya S, Chowdhury JR
Chittaranjan Natl. Cancer Res. Center, 37 S.P Mookherjee Road, Calcutta 700026, India
Indian J Med Res; 74:904-906 1981

Human chorionic gonadotropin (hCG) has been determined by specific radioimmunoassay in the sera of subjects bearing a variety of malignant and nonmalignant lesions. The placental hormone was detected in 59% of the malignant conditions the highest percentage of detectability being 65% in cancer of cervix, followed by 44.8% in breast cancer. (Author abstract) (7 Refs)

41. ESTROGEN RECEPTORS IN CANINE MAMMARY TUMORS.

MacEwen EG, Patnaik AK, Harvey HJ, Panko WB
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Cancer Res; 42(6):2255-2259 1982

The presence of estrogen receptor in 67 canine mammary lesions was correlated with pathological features of the disease. All tissue specimens were analyzed for estrogen receptor content by a sucrose gradient ultracentrifugation method previously used in analyzing human breast cancer cytosols. Pathological features of the tissues were assessed by a veterinary pathologist without knowledge of results of estrogen receptor analysis. Sixty-two (92.5%) of the tissue samples analyzed were classified as epithelial neoplastic lesions, and 38 of these (61.3%), including 24 adenocarcinomas, were estrogen receptor positive (ie, estrogen receptor concentration equal to or greater than 10 fmol/mg cytosol protein). All five of the nonepithelial neoplastic lesions were estrogen receptor negative. Canine and human breast cancers share common histological types and have similar biological behavior. If a significant percentage of canine mammary cancer is also estrogen dependent, the dog may be a useful model for hormonal studies and for the development of models of endocrine therapy for human breast cancer. (Author abstract) (23 Refs)

42. BIOLOGICAL CHARACTERISTICS AND ESTROGEN AND PROGESTERONE RECEPTORS IN MAMMARY CARCINOMA INDUCED IN MALE SPRAGUE-DAWLEY RATS BY A SERIES OF INTRAGASTRIC INTUBATIONS OF 7,12-DIMETHYLBENZ(A)ANTHRACENE.

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Cancer Res; 42(6):2434-2439 1982

Biological characteristics and estrogen (ER) and progesterone (PR) receptors were studied in male mammary carcinomas induced by 7,12-dimethylbenz(a)anthracene (DMBA) in male inbred Sprague-Dawley rats (MM). DMBA-induced carcinomas in females (MF) were used as controls. In 26 of 44 female rats given 20 mg DMBA once by gastric intubation at 50 days of age, MF with microscopic characteristics of cystic papillary adenocarcinoma developed 124 +-49 (S.D.) days after challenge. In all of the 42 male rats given 10 mg DMBA at 14-day intervals for 14 wk starting from 28 days of age, MM with microscopic characteristics of medullary adenocarcinoma developed 106 +-21 days after the first intubation of DMBA. The growth of primary MM was unaffected by orchiectomy or estrogen. Eighty to 100% of the MM transplanted in the four groups could grow in intact female rats, ovariectomized female rats, intact male rats, and castrated male rats, while the transplanted MF could grow only in intact female rats. The histology of MM was unchanged in primary and transplanted tumors under various hormonal conditions. ER were present in almost all of the hormone-independent primary and transplanted MM, although the levels for cytosol ER in MM were significantly lower than those in MF. Injection of 10 ug 17beta-estradiol induced marked synthesis of PR in primary and transplanted MM, even 24 and 48 hr after the 17beta-estradiol injection. These findings show that MM are hormone independent but, like hormone-dependent female tumors, contain ER and estrogen-dependent PR. (Author abstract) (24 Refs)

43. PROLACTIN RECEPTORS IN HUMAN BREAST TUMORS.

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JNCI; 68(3):381-383 1982

Prolactin-binding sites were determined in 759 human breast tumor biopsy specimens. Ovine prolactin (oPRL) was used in the binding assay of 659 tumors with 13% of the tumors showing a positive content with more than 1% specific binding. Human prolactin (hPRL) was utilized for 343 tumors with 36% of the tumors binding 1% or greater of the added radioactivity. When human growth hormone (hGH) was used as the labeled ligand in 95 tumors, only 2% of the tumors specifically bound more than 1% of the hGH. A total of 153 tumors were assayed simultaneously with the use of labeled hPRL and oPRL. Whereas 10.4% of the tumors showed the presence of prolactin-binding sites (greater than 1% specific binding) when oPRL was used, an approximately threefold increase (29.4%) in tumors possessing prolactin receptors was revealed when hPRL was used as the labeled ligand. Therefore, hPRL is the preferred ligand for the assessment of prolactin receptor levels in human breast cancer biopsy specimens. (Author abstract) (15 Refs)

44. PROSTAGLANDIN SYNTHESIS AND BINDING IS INCREASED IN REGRESSING NMU MAMMARY CARCINOMA.

Liu SC, Knazek RA
Lab. Pathophysiology, NCI, NIH, Bethesda, MD
Prostaglandins Leukotrienes Med; 8(3):191-198 1982

Nitrosomethylurea-induced mammary tumors of Buffalo rats were used to study the regression after oophorectomy (oox). The amounts of prostaglandin E2 (PGE2) and prostaglandin F2 alpha (PGF2a) isolated from tumor cells membranes increased during the period of tumor growth, peaking 5 days after oophorectomy. The membrane binding of both prostaglandins (PGs) was saturable and reversible, reaching equilibrium after 30 min. The membrane binding of both PGs was 3-4x above baseline values on day 4 after oox. The membrane binding of PGE2 showed low-affinity characteristics during both tumor growth and oox-induced tumor regression. The membrane binding of PGF2a showed high-affinity characteristics during both tumor growth and oox-induced tumor regression; the post-oox increase in specific PGF2a binding was attributed to an increase in the number of PGF2a receptors. The elevated rates of PGF2a synthesis and the regression-associated increase in PGF2a receptors suggest that PGF2a may play a significant role in hormone-dependent mammary tumor regression. (22 Refs)

45. SIMULTANEOUS DETERMINATION OF STEROID HORMONES IN THE CIRCULATION AND IN TUMOR TISSUE OF PATIENTS WITH BREAST CANCER (MEETING ABSTRACT)

Vallent K, Feher T, Bodrogi L
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VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

In order to obtain information whether steroid hormone availability during tumorigenesis in breast cancer can be characterized by hormone concentration of the general circulation, simultaneous steroid determinations were performed by means of sensitive radioimmunoassays. Estrogens, progesterone, testosterone, androstenedione and dehydroepiandrosterone levels were measured in tumor tissues obtained by surgical treatment of patients. The results were compared with those in peripheral blood. The present findings showed that the actual hormone concentration in serum appears to be an inappropriate measure for hormone availability in breast cancer, since the steroid contents of tumor tissues were 2 to 12 times higher than those in the circulation. In addition, while hormone levels in blood remained practically unchanged, significant differences in the steroid concentration only of tissues could be found when malignant transformation in the cell-systems occurred. (no Refs)

46. HUMAN PROLACTIN AND HUMAN GROWTH HORMONE ALTER CELL SHAPE AND PROLIFERATIVE RATE OF HUMAN BREAST CANCER CELLS IN CULTURE (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:933 1982

The role of prolactin and growth hormone in the etiology of human breast cancer is unclear. Therefore, the biological effects of these hormones on a human breast cancer cell line, T47D, were examined. T47D cells contain a high concentration of receptor sites that bind human prolactin(hPRL) and human growth hormone(hGH). When T47D cells were maintained on plastic substratum, they grew as a 'cobblestone' monolayer and assumed a flat, polygonal shape. However, when cultured in the presence of hPRL or hGH(10 ng/ml to 1 ug/ml), and 1 ug/ml each of hydrocortisone(H), insulin(I), and triiodothyronine(T3), T47D cells became round; the cells were loosely attached to the plastic substratum and they aggregated into large clusters. Such changes were not observed if only hPRL or hGH were present, or if only HIT3 were present, indicating that hPRL and hGH require the synergism of the other three hormones(HIT3) to induce the shape change in T47D cells. Another lactogenic hormone, ovine prolactin, produced a similar effect as hPRL and hGH, whereas non-lactogenic hormones such as ovine growth hormone and human luteinizing hormone had no effect on the T47D cells. As well as having an altered shape, T47D cells proliferated twice as fast in serum-free medium supplemented with HIT3 only; T47D cells failed to proliferate in serum-free medium not supplemented with hormones. (1 Ref)

47. A NEW MARKER FOR HORMONAL RESPONSIVENESS OF RAT MAMMARY TUMORS (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:910 1982

We previously reported a mammary-specific, Ca++-stimulated ribonuclease (Ca++-RNase) whose activity in normal mammary gland parallels the degree of differentiation. To determine whether this enzyme can serve as a marker for hormonal responsiveness, we have assayed the activity in a series of rat mammary tumors of varying orgin. RNase activity of an ammonium sulfate extract prepared from whole tissue homogenate was assayed under various ionic conditions, using (3H)poly(U) as substrate. Although the rate of poly(U) degradation varied according to the ionic conditions of the assay for a given tumor extract and also between tumor extracts under the same assay conditions, a general pattern emerged. In MT/9, MT/9a, DMBA 1, DMBA 8, DMBA 14 and R3230AC tumors, the activity assayed in the presence of CA++, or Ca++ plus EDTA, reflecting Ca++-RNase activity was 4 to 5 times higher than the activity assaysed with Mg++ and 100 to 700 times that in the presence of EDTA alone. These tumors are all known to be estrogen-responsive mammary adenocarcinomas. High Ca++-RNase activity was also present in the estrogen-sensitive 3M2N squamous cell carcinoma. Conversely, RNase activity assayed with Ca++ present was lower than that with either Mg++ or no added ion in MAMF2-TC, SMT-2A and 13762 mammary tumors, all undifferentiated, poorly differentiated or estrogen unresponsive mammary carcinomas. The same is true for mammary fibroadenomas. These results show that Ca++-RNase, which is easily detected in crude tumor extracts, is a useful marker in characterization of rat mammary tumors with respect to estrogen responsiveness. (no Refs)

48. ABNORMAL OXIDATIVE METABOLISM OF ESTRADIOL IN WOMEN WITH BREAST CANCER.

Schneider J, Kinne D, Fracchia A, Pierce V, Anderson KE, Bradlow HL, Fishman J
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Proc Natl Acad Sci USA; 79(9):3047-3051 1982

The three dominant oxidative biotransformations of estradiol were examined in 10 normal women and 33 females with breast cancer by using a recently devised radiometric method. Estradiol tracers, labeled with 3H specifically in the 17alpha, C-2, or 16alpha position, were used to measure both the rate and extent of 17beta-ol oxidation (the initial metabolic step) and the subsequent 2-and 16alpha-oxidative reactions. The mean +-SEM values for the extent of estradiol metabolism at these three specific sites were 76.9 +-5.3%, 31.1 +-4.0%, and 9.3 +-0.8%, respectively, in normal subjects. Corresponding data in patients with breast cancer - ie, 73.0 +-4.2%, 32.7 +-2.7%, and 14.9 +-1.5% - revealed a significantly greater extent of 16alpha-hydroxylation in the latter population. Because of the 16alpha-hydroxylated compounds (including estriol) are themselves potent estrogens, these changes may have important hyperestrogenic consequences that could have a bearing on the etiology of the disease. (Author abstract) (36 Refs)

49. IMMUNOREACTIVE PROLACTIN IN EPITHELIAL CELLS OF NORMAL AND CANCEROUS HUMAN BREAST AND PROSTATE DETECTED BY THE UNLABELED ANTIBODY PEROXIDASE-ANTIPEROXIDASE METHOD.

Purnell DM, Hillman EA, Heatfield BM, Trump BF
Dept. Pathology, Sch. Medicine, Univ. Maryland, Baltimore, MD, 21201
Cancer Res; 42(6):2317-2324 1982

A rabbit antiserum to ovine prolactin was used with the peroxidase-antiperoxidase method to search for immunoreactive prolactin in normal and pathological human breast and prostate. The immunostaining of pituitary cells appeared specific for prolactin since both ovine and human prolactin abolished immunostaining when they were added to the anti-prolactin serum. We stained sections of normal breast and normal prostate. Results suggested that the immunostaining of normal breast and prostate was related to the presence of immunoreactive prolactin in epithelial cells of these organs. In prostate, immunostaining was confined to the secretory cell population. In breast, immunostaining seemed to occur throughout the breast parenchyma. The immunostaining of normal breast epithelium was markedly heterogeneous. This was less pronounced in normal prostate epithelium. Sixty-four percent of the primary prostate adenocarcinomas which were examined showed strong staining reactions with anti-prolactin serum. Two of three metastatic tumors of prostate origin had similar strong staining reactions. Infiltrating duct carcinomas of the breast were strongly stained with anti-prolactin serum, but most breast fibroadenomas were not stained. None of seven adenocarcinomas of the colon tested as controls were stained by anti-prolactin serum. The results suggested that the immunostaining of breast and prostate carcinomas was related to immunoreactive prolactin. The results reported here emphasize the value of the peroxidase-antiperoxidase method in the study of hormone target organ interactions as well as in retrospective studies of pathological materials. (33 Refs)

50. TUMOR CELL GROWTH FACTOR(S) ASSOCIATED WITH AN ESTROGEN-RESPONSIVE RAT MAMMARY TUMOR GROWING IN VIVO (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:936 1982

Growth factors have been identified in extracts of MTW9/PL rat mammary tumor cells growing in vivo in response to estrogens. MTW9/PL tumors from intact females and from both estrogen treated castrated females and males had equivalent growth activity. Tumor extract protein added to serum-free DME at 10 ug/ml promoted significant MTW9/PL growth; 100 to 200 ug/ml replaced 75 to 100% of MTW9/PL serum requirement. Molecular properties of the tumor associated growth activity appear to be distinct from mammary growth factor activities in rat uterine, kidney, and pituitary tissues. The tumor activities show apparent molecular weights of 80,000 and 50,000 daltons on G-100 Sephadex and by heat, protease, and pH treatment, appear to be proteins. These activities are not due to residual serum and are not replaceable by known growth factors or hormones. Estrogens appear to influence directly growth factor activity level in MTW9/PL tumors since ovariectomy led to tumor regression and activity lower than that of tumors which are hormone autonomous or are growing in intact females. Our data suggest: 1) MTW9/PL tumor growth factors are related to estrogen levels in vivo; 2) autonomous tumors may produce growth factors continuously; 3) transformation from normal mammary gland to the neoplastic state includes the appearance of tumor associated growth factor. (no Refs)

51. CORRELATION BETWEEN SERUM SEX HORMONE BINDING GLOBULIN (SHBG) LEVEL AND HORMONE DEPENDENCY OF HUMAN BREAST CANCER (MEETING ABSTRACT)

Vincze B, Szamel I, Svastits E, Hindy I, Kerpel-Fronius S, Eckhardt S
National Institute of Oncology, Budapest, Hungary
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Serum SHBG binding capacity for estradiol was studied in vitro at 4C by saturation analysis. Dextran-coated charcoal (DCC) was applied for the separation of protein-bound and free hormone. The cytoplasmic estradiol receptor (ER) binding capacity was determined by saturation analysis using DCC technique. The kinetic parameters of estradiol-SHBG and ER complexes, as well as the number of binding sites were calculated from a modified Scatchard plot. The serum SHBG levels in 6 premenopausal (37 +/-8 pmol per ml) and 12 postmenopausal (45 +/-16 pmol per ml) women bearing ER positive breast tumor were significantly higher than the levels of 6 premenopausal (20 +/-9 pmol per ml) and 6 postmenopausal (17 +/-4 pmol per ml) patients with ER-negative tumor. It was observd that the SHBG binding capacity before the initiation of tamoxifen treatment was higher in those patients who would respond to therapy. According to our preliminary results serum SHBG titer seems to be a reliable indicator of hormone dependency of breast cancer. (no Refs)

52. STEROID RECEPTORS IN BREAST ANGIOSARCOMA (MEETING ABSTRACT)

Brentani MM, Oshima CT, Nagai MA, Lemos LB
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Proc Am Assoc Cancer Res; 23:937 1982

Mammary angiosarcoma is a rare, highly malignant tumor. The high rate of having the onset of lesions during pregnancy and the coincidence of the peak age incidence of the patients with the peak age of reproduction suggest that the tumor may be hormone dependent. We have determined estrogen, progesterone and glucocorticoid receptors in two cases of angiosarcoma of the breast. Estrogen receptors were present in both tumor cytosols, but in low concentration (14.0 and 8.2 fmol/mg of protein). Progesterone receptor was present, in one of two tumors assayed (20.0fmol/mg of prot). Occupied nuclear estrogen receptors have been found in the nuclear extracts of both tumors. Unoccupied nuclear receptors were found only in the progesterone positive tumor. Both cytosols have glucocorticoid receptors (60.0 and 12.0 fmol/mg of protein). Density gradient analysis suggested that glucocorticoid and estrogen binding was located predominantly in the 6S and 7 to 8S regions, whereas receptor for progesterone sedimented at 4S. Density gradient analysis suggested that glucocorticoid and estrogen binding was located predominantly in the 6S to 8S regions, whereas receptor for progesterone sedimented at 4S. (no Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

53. THY-1 ANTIGEN ON NORMAL AND NEOPLASTIC RAT MAMMARY TISSUES: CHANGES IN LOCATION AND AMOUNT OF ANTIGEN DURING DIFFERENTIATION OF CULTURED STEM CELLS.

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JNCI; 68(5):799-811 1982

With the use of immunofluorescent and immunocytochemical techniques on histologic sections of mammary glands from inbred WF rats, the thymocyte differentiation antigen (Thy-1) was identified partially on and immediately adjacent to the myoepithelial cells of ducts and alveoli. This antigen was absent from epithelial cells lining such structures. Some fibroblastic cells external to these structures also bore Thy-1. During glandular development the intensity of fluorescence due to the binding of Thy-1 antibodies increased as the myoepithelial cells matured. Similarly, mammary adenocarcinomas induced by 7,12-dimethylbenz[a]anthracene (DMBA) and N-methyl-N-nitrosourea contained elongated, presumptive myoepithelial cells that demonstrated varying degrees of Thy-1 immunofluorescence. This phenomenon was qualitatively mimicked by cultured cell lines from normal and DMBA-induced tumors. Elongated myoepithelial-like and fibroblast-like cells possessed Thy-1, whereas the cuboidal epithelial cell lines failed to express this antigen on the cell surface. Measurement of the relative number of Thy-1 molecules per cell by antiserum absorption techniques suggested that a neoplastic stem cell line, rat mammary (Rama) 25, contained about 3 x 10(5) Thy-1 molecules per cell in a form not directly accessible at the cell surface to anti-Thy-1 antibodies; the number of cryptic Thy-1 molecules was reduced when this cell line differentiated to alveolar-like cells in culture. However, when this cell line differentiated to myoepithelial-like cells, approx 5 x 10(6) molecules per cell were exposed to anti-Thy-1 antibodies with a concomitant reduction of the cryptic pool. Morphologic maturation of elongated, myoepithelial-like cell line variants was also accompanied by increased surface Thy-1 fluorescence. Thus some of the myoepithelial cells in normal glands and tumors may arise by differentiation of epithelial stem cells and a spectrum of maturation states of the myoepithelial cell may exist as monitored by cellular morphology and surface Thy-1 expression. (Author abstract) (44 Refs)

54. CHARACTERIZATION OF A MONOCLONAL ANTIBODY REACTIVE WITH A SUBSET OF HUMAN BREAST TUMORS.

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JNCI; 68(5):719-728 1982

Fusion of spleen cells, from mice immunized against the human hormone-dependent breast cancer cell line ZR-75-1, with murine myeloma cells resulted in the establishment of a hybridoma cell line, HY59-H10(H59). The purified monoclonal IgM produced by the hybridoma reacts with the most differentiated human breast tumor cell lines but not with cells derived from normal breast secretions or with numerous other malignant cell lines. Of 106 biopsy specimens examined, H59 bound to 54% of malignant breast specimens, to 83% of fibroadenomas, and to 82% of specimens containing fibrocystic disease. Binding could not be detected in uninvolved breast tissue. (Author abstract) (52 Refs)

55. IMMUNOGENICITY OF SPONTANEOUSLY-ARISING RAT TUMOURS IN SYNGENEIC HOSTS (MEETING ABSTRACT)

Embleton MJ, Middle JG
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VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Forty-four tumors of various histological types which arose spontaneously in inbred WAB/Not rats were established as transplanted tumor lines in syngeneic hosts. Their immunogenicity was assessed by challenge-protection tests in which syngeneic rats were immunized against tumor from early transplant generations, followed by challenge with tumor cell inocula just sufficient to achieve tumor growth in untreated controls. Three tumors (a squamous cell carcinoma, a mammary carcinoma and a fibrosarcoma) were found to be moderately immunogenic, inducing specific anti-tumor immunity at a level equivalent to that commonly observed with chemically-induced tumors. Four more tumors (two sarcomas and two mammary carcinomas) produced very weak, barely detectable immunity to challenge and the remainder appeared to be completely non-immunogenic. It is concluded that the majority of spontaneous rat tumors lack rejection antigens recognized by the host, but the fact that some do so supports the continuation of efforts to enhance anti-tumor immune mechanisms against human cancer. (no Refs)

56. CELL SURFACE ANTIGEN COMMON TO HUMAN BREAST CARCINOMA CELLS AND NORMAL TROPHOBLAST (MEETING ABSTRACT)

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VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Rabbit heteroantisera have been raised against both x-irradiated human MCF-7 breast carcinoma cells and against human trophoblast microvillous plasma membrane preparations isolated from normal full-term placenta. These antisera were then absorbed several times with immobilized human term pregnancy sera, placental alkaline phosphatase, placental ferritin as well as human peripheral blood leukocytes. Immuno-histological studies on cryostat sections of human placenta and breast carcinoma tissue have shown reactivity of both the adsorbed antisera with normal trophoblast and breast carcinoma cells in tissue sections but no reactivity with other normal human tissue. Further adsorption experiments have also shown that the cross-reactive antigen is represented on human Jar choriocarcinoma cells and Av3 amniotic cell. An indirect radio-isotopic antibody assay with MCF-7 and Elco breast carcinoma cells has been used to confirm the detection of a cell surface antigen common to breast carcinoma cells and normal trophoblast but not to normal adult tissue. (no Refs)

57. NATURAL KILLER (NK) ACITIVITY IN PERIPHERAL BLOOD LYMPHOCYTES OF PATIENTS WITH BENIGN AND MALIGNANT BREAST DISEASE (MEETING ABSTRACT)

White DM, Jones DB, Cooke T
Department of Pathology, Southampton General Hospital, Southampton, England
Br J Radiol; 58(11):812 1981

It is well established that lymphocytes from unimmunized individuals may be cytotoxic for cell cultures of neoplastic origin. This co-called natural killer (NK) activity is considered important in the surveillance against spontaneously arising tumors. However, no differences in NK activity have been reported between established early carcinomas and controls. In this study, lymphocytes prepared from preoperative blood samples of women with benign and malignant breast disease were tested at varying effector to target ratios for cytotoxic activity against the NK-sensitive erythromyeloid line K562. A significant reduction of NK activity was observed between carcinoma patients and the control group. When the carcinoma group was further divided into pre- and postmenopausal patients, the significant reduction was found to be present only in the premenopausal woman. The levels of NK activity in patients with benign breast disease were not significantly different from controls, irrespective of menstrual status. There was no correlation between NK activity and tumor size, estrogen receptor or lymph node status. The effects of estrogens on NK activity and the immunological status of patients will be discussed with respect to the results. (no Refs)

58. DEMONSTRATION WITH MONOCLONAL ANTIBODIES OF AN UNUSUAL MONONUCLEAR CELL INFILTRATE AND OF LOSS OF NORMAL EPITHELIAL MEMBRANE ANTIGENS IN HUMAN BREAST CARCINOMA (MEETING ABSTRACT)

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Br J Radiol; 58(11):811 1981

Present histological and other laboratory criteria are inadequate in predicting the wide variation in biological behavior of breast carcinoma. We have used monoclonal antibodies (MCAbs) raised in this laboratory and directed at two normal differentiation antigens of breast epithelium to see if breast carcinomas can be subdivided by whether or not they express these normal cell surface antigens. One of the MCAbs used detects the human Thy-1 antigen and was of particular interest as Thy-1 has been implicated in cell-to-cell adhesion in rodents. The other MCAb is directed at an antigen also present on brain, granulocytes and T lymphocytes (BGTAg). A third MCAb, directed at a molecule expressed exclusively on leukocytes, identified leukocyte infiltrates in the tumors. Using immunofluoresence on frozen sections, of 16 carcinomas studied, only 2 expressed Thy-1 and 3 the BGTAg. Of greater interest, however, was the finding that the majority of lymphocytes infiltrating some carcinomas were Thy-1 positive. This was entirely unexpected as Thy-1 is absent from human blood lymphocytes and found only sparsely in normal lymphoid tissue. Our studies therefore demonstrate that it is possible to differentiate histologically indistinguishable carcinomas on the basis of differentiation antigens. These findings raise intriguing questions regarding the nature of the mononuclear cell infiltrate. A prospective long term study has been started to see whether or not the presence of these and other antigens correlates with the clinical behavior of breast carcinomas. (no Refs)

59. IGA CONTAINING IMMUNE COMPLEXES IN DOGS BEARING SPONTANEOUS MAMMARY ADENOCARCINOMA (MEETING ABSTRACT)

Balint J, Nagai T, Ikeda Y, Meek K, Terman DS
Baylor College of Medicine, Houston, TX, 77030
Fed Proc; 41(3):312 1982

Sera from dogs with mammary adenocarcinoma (MA) were assayed for the presence of immune complexes (IC) and physicochemical composition of these complexes was assessed. Employing 125I anti-canine IgG, as indicator, elevated levels of C1q binding were detected in sera of dogs with MA but not in normal canine sera or sera of dogs with various other tumors. Polyacrylamide gel electrophoresis analysis of IC isolated by G-200 fractionation and protein A affinity chromatography revealed the presence of a dense polypeptide band corresponding to the alpha chain of IgA which was present only in MA sera but not in normal dog sera or sera from dogs with other tumors. Employing monospecific radiolabeled anti-canine IgA as indicator in solid phase C1q binding radioimmunoassays, significantly elevated levels of C1q binding were detected in 5 of 8 MA sera but not in sera of normal dogs or other tumor bearing dogs. Sera from MA bearing dogs treated with 5% polyethylene glycol and subjected to sucrose density gradient ultracentrifugation revealed IgA containing IC in fractions greater than 7S to greater than 19S. Findings suggest that IC are present in sera of dogs with MA; IgA is a major and unique component of these complexes and hence may play a significant role in the development and evolution of the canine immune response to mammary adenocarcinoma. (no Refs)

60. AUGMENTATION OF NATURAL KILLER CELL ACTIVITY IN NORMAL AND TUMOR BEARING BALB/C MICE BY LEVAMISOLE (MEETING ABSTRACT)

Laing CA, Japal KM
Howard University Cancer Center, Washington, DC, 20060
Proc Am Assoc Cancer Res; 23:1060 1982

Natural killer cell (NK) activity is an important factor in the immune constituent of young mice and seems to play a role in immune surveillance mechanisms against tumors. Levamisole (LMS) had exhibited immunoregulatory and anti-tumor properties but its effects on NK activity has not been investigated. Whether LMS exert any regulatory function on NK activity in 8 wk old male BALB/c mice was the question posed in this study. Two groups of mice were inoculated with 1x10(6) viable cells (in minimal essential medium) of the 50th transplant generation of a MTV induced mammary tumor which originated from a spontaneous tumor in multiparous BALB/cfC3H female. At the time of inoculation of tumor cells and at 24, 48, and 72 hr thereafter, one group was inoculated with LMS (50 mg/kg of body weight). A third group received LMS alone; controls received no treatment. Administration of LMS caused a significant increase in NK activity of normal non tumor bearing mice above controls. In mice inoculated with tumor cells alone, an increase in NK activity was observed above controls. This could be further augmented above controls by LMS administration in tumor bearing mice. LMS augmentation of NK activity was detected as early as 48 hr and up to 144 hr post inoculation. (no Refs)

61. TUMORICIDAL MACROPHAGES (MS) ISOLATED FROM MURINE MAMMARY TUMORS THAT DIFFER IN BIOLOGICAL BEHAVIOR (MEETING ABSTRACT)

Loveless SE, Munson AE, Heppner GH
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:1034 1982

A number of distinct subpopulations have been isolated from a single BALB/cfC3H mouse mammary tumor and been shown to differ with respect to growth properties, immunogenicity and metastatic potential. We have compared various aspects of macrophage activity in these subpopulations in order to determine which may relate to tumor behavior. Three subpopulations were chosen for more detailed study: 67 and 68H are slow-growing, non-metastatic lines, whereas 4.10.4 is fast-growing and highly metastatic to lung. Line 68H is non-immunogenic in BALB/cfC3H mice, whereas the other lines are immunogenic. Subcutaneous tumors of these sublines were removed, enzymatically disaggregated and M content determined by morphology, Fc rosettes and latex bead phagocytosis. Ms accounted for 22, 18 and 25 of dissociated cells from lines 67, 68H and 410.4, respectively. No significant correlation was observed between M content and tumor size, weight, or age. Purified intratumoral M were tested for their ability to lyse radiolabeled syngeneic tumor cells in vitro. Significant M-mediated tumoricidal activity was detected in 8 of 8 experiments with 4.10.4, but in only 1 of 5 and 4 of 8 tests for 67 and 68H, respectively, at effector:target ratios ranging from 1:1 to 50:1. Therefore, differential tumoricidal activity, rather than percentage, distinguishes the Ms of these different neoplastic subpopulations. (no Refs)

62. PATTERNS OF LYMPHOCYTE INFILTRATION IN TUMOR SUBLINES OF A SINGLE MAMMARY ADENOCARCINOMA (MEETING ABSTRACT)

Rios A, Laux D, Heppner G
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:1021 1982

Previous reports from our laboratory have described isokinetic gradient separation of infiltrating host cells from mouse mammary tumors. The present study is a further characterization of the infiltrating cells and the lymphoid populations present in regional and distant lymph nodes of tumor bearing mice. Three tumor lines, that differ in growth properties, immunogenicity, and ability to metastasize, and which were derived from a single BALB/cfC3H mammary adenocarcinoma, were used. Single cell suspensions were separated on isokinetic gradients and the purified populations were tested for reactivity with anti-lymphocyte serum (ALS) and monoclonal antibodies to mouse Thy 1.2, Lyt 1.2 and Lyt 2.2 antigens. In the lymphoid fraction, the percent cells recovered and percent ALS positive, respectively, were 45% and 80% for line 68H; 39% and 80% for 410, and 12% and 90% for 168. Tumors 68H contained high numbers of Lyt 1.2+ cells and low numbers of Lyt 2.2+ cells. Four hundred ten tumors were very low in Lyt 1.2+ cells, but moderate in Lyt 2.2+ cells, and 168 tumors had moderate numbers of Lyt 1.2 cells and were very high in Lyt 2.2+ cells. Variation was also observed in the lymph node populations with generally dominant Lyt 2.2+ cells in the regional lymph nodes, whereas the distant lymph nodes reflected the pattern of lymphocytes purified from the tumor. Thus, there is a distinct variation in pattern of infiltrating cells among these three tumor lines despite their common parental origin. The relationship of these patterns to immunogenicity is not direct. (no Refs)

63. EFFECT OF CEA PRODUCTION ON THE SENSITIVITY OF HUMAN TUMOR CELLS TO LYSIS BY NATURAL KILLER CELLS (MEETING ABSTRACT)

Clark DA, McCulloch PB, Deat PB, Liao SK
McMaster University, Hamilton, Ontario L8N 3Z5, Canada
Proc Am Soc Clin Oncol; 1:C-136 1982

Addition of BCG to combination chemotherapy (5-fluorouracil + cyclophosphamide + adriamycin) in our patients with advanced breast cancer produces significant benefit only in the subgroup of patients who have the fetal antigen CEA (carcinoembryonic antigen) elevated in their pre-therapy plasma samples. BCG therapy had no consistent effect on the response to DNCB (dinitrochlorobenzene), recall antigen skin tests, or in vitro response to PHA (phytohemagglutinin). Since BCG therapy may augment the activity of natural killer cells, we have tested different clones derived from an adenocarcinoma cell line that release different amounts of CEA into their supernatant to determine if CEA production correlates with sensitivity to lysis by NK cells. A high CEA-producing line of HCT-8 cells proved significantly more sensitive to lysis in a 20 hr 51 Cr-release assay than did a low CEA-producing line. Saturation of the assay with alpha-interferon or addition of anti-interferon antibody to the assay did not eliminate the difference in sensitivity to lysis, and mixing experiments confirmed that the higher sensitivity to lysis by the CEA producing line was not due to induction of NK activity. Limiting dilution analysis showed that the high CEA line reacted with a much larger population of blood NK cells. A greater proportion of NK cells killing high CEA line cells were E rosette positive. Theophyline induced enhancement of expression of surface CEA-like antigen was associated with an increase in sensitivity to lysis by NK cells. (no Refs)

64. LONG TERM FOLLOW UP OF DOGS WITH SPONTANEOUS MAMMARY TUMORS TREATED WITH EX-VIVO PLASMA PERFUSION OVER STAPH AUREUS COWAN STRAIN I (SAC) (MEETING ABSTRACT)

Messerschmidt G, Bowles C, Alsaker R, Deisseroth A
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Proc Am Assoc Cancer Res; 23:1103 1982

A previous study has reported the anti-tumor activity of ex-vivo immunoperfusion. These dogs have been followed without further perfusion for up to 844+ days. Ten dogs were treated, 5 responded with 61%+ tumor reduction and 5 were non-responders. Five additional dogs were controls without SAC. No non-responder dog has lived (mean survival 245 days). Responder dogs have survived a mean of 435 days with 2 dogs alive a 765+ and 844+ days. Three of 5 responders obtained a complete remission (CR) as assessed by the followable skin site -1 with perfusion alone, 2 with surgical biopsy after reduction by perfusion of 88% and 94%. Mean time from tumor response to tumor regrowth was 251 days. Of the 3 CR dogs, 1 died day 18 from pneumonia and visceral tumor, 1 recurred at day 439, and one remains disease free at 765+ days. All non-responder dogs had some tumor reduction that lasted an average of 41 days. Though responders survived longer than non-responders, their survival was not longer than controls. Tumor bulk was comparable in the controls and responders which was less than non-responders. Also, 3 of 5 non-responders had massive metastatic disease compared to metastasis in 1 control and 1 responder. Comparing pre- and post-treatment biopsies, responders had increases in neutrophil and macrophage infiltration whereas the control dogs had no change. (no Refs)

65. MITOGEN-INDUCED BLASTOGENESIS AND RECEPTOR MOBILITY INHIBITION BY BREAST CANCER SERUM WITH ELEVATED OROSOMUCOID (ALPHA1-ACID GLYCOPROTEIN) LEVELS.

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JNCI; 68(5):779-783 1982

Sera from cancer patients have been shown to suppress normal lymphoid cell responsiveness in vitro. In the present study, sera from breast cancer patients were demonstrated to be inhibitory to the concanavalin A (Con A)-, Proteus vulgaris-derived phytohemagglutinin-, and pokeweed mitogen-induced blastogenic responses of normal lymphoid cells. Orosomucoid (OR) (alpha1-acid glycoprotein), an acute-phase reactant, was elevated in these sera, and a positive correlation existed between the OR level in the sera and its immunosuppressive capacity. When normal lymphoid cells were reacted in fluorescein isothiocyanate-labeled Con A, cells that had been preincubated in breast cancer sera known to contain an elevated level of OR showed a significant decrease in Con A receptor mobility as compared to the receptor mobility of the same lymphoid cells preincubated in normal sera. Thus a component(s) from the sera of breast cancer patients had the capacity to inhibit lymphocyte activation. This inhibition might have resulted from an interaction of OR with the cell membrane. (Author abstract) (34 Refs)

66. MODULATION OF ANTIGENIC PRESENTATION BY CELL FUSION (MEETING ABSTRACT)

Tachibana T, Kanbe M, Oshima H, Ishikawa S, Dei T
Department of Immunology, Tohoku University, Sendai, Japan
VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

A somatic hybrid cell line which was formed between C3H/He ascitic mammary tumor FM3A cell and syngeneic L cell, immunized specifically syngeneic hosts against subsequent lethal parental tumor challenge. The immune resistance induced by inoculation of viable and irradiated hybrid tumor was superior to that induced by irradiated parental tumor cells. The resistance seemed to be specific for the MM antigen, tumor associated surface antigen expressed on some ascitic mammary tumor cells. Generation of CTL in the spleen of C3H/He mice by inoculation of hybrid cells was contrasted with preferential antibody production by irradiated tumor cells, although cytotoxic non-T cells, adhering to Sephadex G-10 were appeared in the spleen of mice immunized with irradiated tumor cells. Antigen recognition of CTL generated by hybrid cells seems to be most MHC-restricted from the data on direct cytotoxicity and cold target inhibition test by using various histoincompatible MM antigen positive cells. (no Refs)

67. MONOCLONAL ANTIBODIES TO TUMOR-ASSOCIATED ANTIGENS (TAAS) DEFINE HETEROGENEITY OF HUMAN MAMMARY TUMORS (MEETING ABSTRACT)

Nuti M, Hand PH, Colcher D, Schlom J
National Cancer Institute, National Institutes of Health, Bethesda, MD, 20205
Proc Am Assoc Cancer Res; 23:1056 1982

Murine monoclonal antibodies, prepared against human metastatic mammary tumor cells, demonstrate differential expression of several TAAs among various mammary carcinomas and within a given tumor mass. Using the immunoperoxidase technique on serial sections of 45 primary mammary carcinomas, a spectrum of antigenic expression of TAAs was observed: 13 percent of the tumors reacted with all of a panel of five monoclonal antibodies, while 20 percent of the mammary tumors scored negative with all five antibodies. The remaining 30 tumors could be divided into eleven additional groups based on their differential reactivity with some, but not all, of the monoclonals. A heterogeneity in antigenic expression of mammary tumor cell populations within a given tumor mass was also observed. Heterogeneity of TAA expression was also observed in established mammary tumor cell lines. An increase in cell surface binding of one of the monoclonals was associated with cells in S-phase, whereas a decrease in binding was observed at high cell density. Consistent with this finding, MCF-7 mammary tumor cells obtained from four sources could be differentiated from each other by their pattern of surface TAA expression. Human mammary tumors, derived from transplantation into athymic mice, also demonstrated this heterogeneity of TAA expression. Radiolabeled monoclonal antibodies could also be used to detect 'in-situ' human mammary tumors transplanted in athymic mice. (no Refs)

68. COMPARISON OF CHEMOTAXIS OF BONE MARROW CELLS FROM C3H MICE BEARING MAMMARY ADENOCARCINOMA, INFECTION WITH STAPHYLOCOCCUS AUREUS AND NECROSIS (MEETING ABSTRACT)

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Department of Pathology, Loyola University of Chicago, Stritch School of Medicine, Maywood, IL, 60153
Proc Am Assoc Cancer Res; 23:1007 1982

It was previously shown that in vitro chemotaxis toward guinea pig serum of bone marrow cells (BMC) was greater in mammary adenocarcinoma-bearing C3HeBFeJ mice than in normal mice. The magnitude of chemotaxis was correlated with the length of time of growth of primary tumor and with the degree of metastasis in the lung following removal of primary tumor. The finding was shown to extend to another kind of tumor, a fibrosarcoma induced by 3-methylcholanthrene. The present experiment compares chemotaxis of BMC of mice with a four hour infection with Staphylococcus aureus (SA) or subcutaneous injection of turpentine to that from normal mice and mice bearing a mammary adenocarcinoma. Hematoxylin and eosin stains of sections of lesions caused by SA and by turpentine all contained infiltrates of polymorphonuclear cells. Chemotaxis was studied using migration under agarose and by time-lapse photography. The chemotaxis of BMC from mice with necrosis due to turpentine was not significantly different from normal but was less than that from tumor-bearing animals. There was no correlation between percent of polymorphonuclear cells in the bone marrow and the degree of chemotaxis. Chemotaxis of BMC is correlated with presence of tumor and not with infection with SA or necrosis. (no Refs)

69. ISOLATION OF MACROPHAGE SUBPOPULATIONS FROM MOUSE MAMMARY TUMORS BY COUNTERFLOW CENTRIFUGAL ELUTRIATION (MEETING ABSTRACT)

Mahoney K, Fulton A, Loveless S, Heppner G
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:995 1982

Tumors produced from distinct cell lines originally derived from a single, heterogeneous BALB/cfC3H mammary tumor were used as the source of tumor-associated macrophages.

Healthy tumor tissue was cut into 1mm2 pieces with forceps and scalpel. Single cell suspensions were prepared by enzymatic digestion using protease type IX, collagenase type III and DNAse type I in Hank's balanced salt solution (HBSS). Greater than 90% cell viability was achieved. Elutriations were performed in calcium-magnesium-free HBSS with 1.0% newborn Bovine Serum using a Beckman centrifuge and a JE-6B elutriation head. The rotor speed was held at 2225 RPM, while the flow rate was increased as fractions were collected. These conditions produced 5 fractions with elutriation diameters up to 6.4, 9.0, 11.0, 12.0 and 12.7 um; cells larger than this remained in the chamber. Greater than 90% of the 1-5 X 10(8) cells loaded were recovered. Different tumors have distinct elutriation profiles (% of the total cells recovered in each fraction), eg for line 410.4, the values are 23.5 +/-2.8, 29.7 +/-0.8, 28.2 +/-1.2, 7.7 +/-1.0, 3.8 +/-0.6 with 8.0 +/-0.9 in the chamber, whereas for line 67 the values are 15.6 +/-1.1, 14.4 +/-3.2, 38.1 +/-1.8, 21.3 +/-1.8 (for fractions 4 and 5 combined) and 10.8 +/-1.5 in the chamber. Macrophages can be isolated from each fraction by adherence and are distributed differentially among the fractions, although predominantly in fractions 2 and 3. Preliminary data indicate that these same fractions also contain the tumor cell cytolytic macrophages. The macrophage subpopulations also differ in expression of the ectoenzymes leucine aminopeptidase, alkaline phosphodiesterase I, 5' nucleotidase, and in prostaglandin production. (no Refs)

70. CIRCULATING IMMUNE COMPLEXES (CIC) AND ASSOCIATED ANTIGEN IN BREAST CARCINOMA (BC) (MEETING ABSTRACT)

Salinas FA, Wee KH, Silver HK, Ragaz J
Cancer Control Agency of British Columbia and University of British, Columbia Vancouver, British Columbia V5Z 3J3, Canada
Proc Am Assoc Cancer Res; 23:986 1982

We have recently reported on tumor burden and its relationship to antigen concentration, size and composition of CIC in malignant melanoma and ovarian carcinoma. To further understand such interaction we evaluated CIC in 118 BC patients (pts) selected on the basis of objective measurable tumor burden. Pts were grouped as reported earlier: 50 Group (Gp) I pts with no evidence of disease at sampling time, 30 Gp II pts with minimal tumor burden estimated at 5 g, and 38 Gp III pts with known regional or distal metastatic disease. CIC were evaluated by following tests: Fetal liver cell (FLC), Raji-cell, and solid phase ClQ radioimmunoassays (RIA). Results of simultaneous evaluation showed a significant correlation among test results (r equals 0.84, p less than 0.01, Spearman test). Also significant was the mean +/- se, expressed as ug aggregated human IgG equivalent /ml serum (ug/ml), for FLC equals 32 +/-4, Raji equal 28 +/-4, and ClQ equals 26 +/-8, as compared to 95 normal control sera (11 +/-1). Elevated (mean + 2 SD) CIC were observed in 28/118 (24%), 27/118 (27%) and 5/15 (33%) by the FLC, Raji, and ClQ RIA respectively. BC pts demonstrated a non-linear relationship with tumor burden. From this study three elevated (10-fold) CIC samples were selected for breast cancer associated antigen (BCAA) isolation by a Raji-cell bound CIC method as reported earlier. Isolated BCAA depicted a common pI 5.0 for all Gp's with an extra band at pI 8.5 for Gp III serum. These results indicate that BCAA represents a proven source of specific biological molecules useful for developing clinical monitoring and diagnostic techniques for BC pts management. (1 Ref)

71. INTERFERON AS MODIFIER OF ESTROGEN RECEPTORS IN CANCER TISSUES (MEETING ABSTRACT)

Dimitrov NV, Myer C, Einhorn S, Strander H, Cantell K
Michigan State University, Lansing, MI, 48824
Proc Am Assoc Cancer Res; 23:946 1982

The purpose of these studies was to determine the effect of human interferon on the activity of estrogen binding protein in breast cancer tissue. Human breast cancer tissues, a variety of breast cancer cell lines and normal uterus as a control were used as a source of estrogen binding protein. Tissue and cell homogenates were incubated with various doses of highly purified human leukocyte interferon (IFN). The effect of the IFN was recorded as two-three fold increase in the cytosol estrogen receptors. The optimum response was obtained with doses ranging between 10 and 1000 U/mL of incubation medium. The escalation of the dose up to 5000 U/mL did not increase or inhibit the binding activity. Cytosol fractions with zero or low binding activity did not respond to IFN treatment. Addition of antibodies against IFN resulted in abrogation of the IFN effect. Incubation of homogenates with mock IFN did not show any increase in the estrogen binding activity. These experiments indicate that the increase of the estrogen receptor activity is due to IFN and not to possible contaminants. Preliminary results from experiments with a variety of IFN-alpha and IFN-beta preparations indicated no difference in the biological modification of the estrogen binding protein. The increase of estrogen receptors activity in breast cancer may have an important clinical application if the effect of IFN in vivo is identical to that obtained in our experiments. (no Refs)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

72. ENDOGENOUS ONCOGENIC TYPE B VIRUSES IN MICE.

Komarova EA, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):3-12 1982

Incidence, oncogenicity, and modes of transmission of endogenous mammary tumor type B viruses in different mice strains are reviewed. Biological activity of type B virus was shown to depend upon the virus-host system. The titer of the endogenous virus in the milk depended upon the age and the number of lactations of the females. The incidence of mammary gland carcinoma (MGC) after administration of type B virus depended upon the sensitivity of the mice and the level of natural killer cells. Analysis of specific viral DNA sequences in the cell genome showed the presence of 3-5 provirus copies in high-cancer and low-cancer mice. Recent findings indicated that MGC cells of GR mice contain increased number of the copies of viral genome. The genome of type V endogenous viruses consisted of two subunits. Concentration of phosphoproteins pp20 and p16 in the endogenous viruses was lower than that in the exogenous type B viruses. Expression of the viral genome during spontaneous and induced carcinogenesis depended upon the hormonal status of the host. (77 Refs) (In RUS)

73. SUPPRESSION OF SPONTANEOUS MAMMARY TUMORIGENESIS DESPITE MTV-1 GENE EXPRESSION IN HYBRID AND BACKCROSS C3H-AVYFB X C3H/SM MICE.

Smith GH, Henry TJ, Vlahakis G, Arthur LO
Lab. Molecular Biology, NCI, Bethesda, MD, 20205
Int J Cancer; 29(5):591-598 1982

Mouse mammary tumor virus (MMTV)-specific RNA and antigen content of normal and neoplastic mouse mammary tissue were measured in strains C3H/Sm and C3H-AvyfB in C3H-AvyfB female x C3H/Sm male F1 hybrids and in (C3H-AvyfB x C3H/Sm) x C3H/Sm male backcross segregants. The molecular data, along with the relative mammary tumor incidences, suggest that the endogenous MMTV provirus expression gene Mtv-1 present in C3H mice is fully expressed in the C3H-AvyfB subline but is silent or more probably absent in the C3H/Sm subline. Cessation of translational expression of endogenous MMTV occurred only in the agouti backcross females, suggesting an association between this phenomenon and the agouti locus of C3H/Sm. Evaluation of the relative MMTV RNA content of nucleic and cytoplasmic fractions from C3H/Sm mammary tissues strongly suggests that transport and/or processing of MMTV RNA is defective in these mice. This defect probably accounts for the absence of detectable MMTV antigens in C3H/Sm and agouti backcross mammary tissues and tumors and may contribute to the observed reduction in mammary tumor incidence. (27 Refs)

RADIOLOGICAL ASPECTS OF MAMMARY GLAND CARCINOGENESIS

74. RELATIONSHIP BETWEEN THE ANTITUMOR EFFECT OF HYPERTHERMIA AND IRRADIATION AND THE GENETICAL STRUCTURE OF TUMOR CELLS.

Turbin NV, Aleksandrov NN, Fradkin SZ, Lobko GN, Muravskaia GV, Porubova GM
Inst. Genetics and Cytology, Minsk, USSR
Eksp Onkol; 4(2):50-54 1982

The relationship between the tumor's genotype and sensitivity to irradiation and/or hyperthermia was studied in C3H/Sn mice bearing the paratetraploid mammary gland A4C3H/Sn tumor or paradiploid Ehrlich tumor. On day 10-12 after tumor transplantation, mice were subjected to repeated local microwave irradiation (hyperthermia of 41.5 C) followed by 137Cs gamma irradiation (1,000 rads). Animals were sacrificed 24 hr after the last exposure. The tumors were removed and homogenized, and suspension of tumor cells was injected ip into intact mice. The cytogenetic analysis of the ascitic fluid was carried out on day 8-10 after inoculation. Hyperthermia alone or in combination with gamma irradiation provided inhibition of Ehrlich tumor growth: av duration of mice survival subjected to four hyperthermia exposures alone and in combination with gamma irradiation was 41.1 and 46.0 days, respectively, compared with 28.4 days in controls. A4C3H/Sn tumor was resistant to hyperthermia alone (28.2 days, compared with 30.0 days in controls and 48.0 days after four hyperthermia exposures in combination with gamma irradiation). (21 Refs) (In RUS)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

75. RAT MAMMARY GLAND CARCINOGENESIS AFTER LOCAL INJECTION OF N-HYDROXY-N-ACYL-2-AMINOFLUORENES: RELATIONSHIP TO METABOLIC ACTIVATION.

Allaben WT, Weeks CE, Weis CC, Burger GT, King CM
Div. Carcinogenesis, Natl. Center Toxicological Res., HFT-110, Jefferson, AR, 72079
Carcinogenesis; 3(3):233-240 1982

A single local injection of 2.5 umol of N-hydroxy-N-formyl-2-aminofluorene (N-hydroxy-FAF), N-hydroxy-N-acetyl-2-aminofluorene (N-hydroxy-AAF), or N-hydroxy-N-propionyl-2-aminofluorene (N-hydroxy-PAF) to each of the six left mammary glands of female Sprague-Dawley derived CD rats gave a mammary tumor incidence, after 12 mo, of 53% for the N-acetyl, 41% for the N-formyl and 33% for the N-propionyl derivatives of N-hydroxyl-N-2 aminofluorene. When N-acetyl-2-aminofluorene (AAF) was applied as above there was only an 8% mammary tumor incidence. Arylhydroxamic acid N,O-acyltransferase activity has been demonstrated in the mammary glands of male, and lactating and non-lactating female Sprague-Dawley derived CD rats by means of a nucleic acid binding assay. Mammary gland cytosol catalyzed tRNA adduct formation to a greater extent with N-hydroxy-FAF. AAF was not activated by this enzyme. Ammonium sulfate fractionation demonstrated the presence of two enzymes, one specific for N-hydroxy-FAF, the other specific for N-hydroxy-AAF and N-hydroxy-PAF. Gel filtration chromatography of mammary gland cytosol demonstrated the presence of two enzymes of differing acyl specificity. Mammary gland microsomes catalyzed the formation of tRNA adducts, but only with the N-hydroxy-FAF derivative. Assays that tested the mutagenic potential of the arylhydroxamic acids in Salmonella typhimurium TA-1538 with either mammary gland cytosol or microsomes demonstrated the order of mutagenicity to be N-hydroxy-FAF much greater than N-hydroxy-AAF greater than N-hydroxy-PAF. A similar order of mutagenicity was demonstrated without an external metabolic activation system. These data demonstrate the presence of two distinct enzymes in the rat mammary gland that activate arylhydroxamic acids. (37 Refs)

76. HAEMATOLOGICAL CHANGES IN EXPERIMENTAL TUMOURS.

Ray MR, Guhathakurta S, Chowdhury JR
Dept. Tumor Biology, Chittaranjan Natl. Cancer Res. Center, 37 S.P. Mookerjee Road, Calcutta 700026, India
Indian J Med Res; 74:896-903 1981

To study the effects of transplantable, induced and spontaneous tumors on the hematopoietic system of the host, strain A mice were inoculated ip with 1 x 10(7) Sarcoma 180 and Ehrlich's ascites carcinoma cells, Swiss mice with DBA lymphoma cells with similar inoculation size and DBA/2 mice with 1 x 10(5) L1210 leukemic cells. Tumors were induced in Strain A male mice by subcutaneous injection of 0.3 ml 0.133% 3,4-benzo(a)pyrene in olive oil suspension, and spontaneous mammary tumors were obtained from female C3H mice. Generally, normochromic and normocytic anemia was observed in all the cases at the later phases of tumor progression, although mild to moderate anisocytosis in sarcoma 180, DBA lymphoma, Ehrlich's ascites carcinoma and carcinogen-induced tumor were noticed, and poikilocytosis was significant in L1210 tumor-bearing mice. The lymphoid-myeloid ratio was reversed to 1:4 and a progressive neutrophilia with moderate shift to the left occurred with increasing body burden of tumor cells in all the tumor strains. Marked leukocytosis was a rule and a broad spectrum combinations of antibiotics failed to suppress high leukocyte count. Thrombocytosis with heterogeneous population of platelets was evident in all the cases, though in Sarcoma-180, Ehrlich's ascites carcinoma and DBA lymphoma-bearing mice the clotting and bleeding time were prolonged. (Author abstract) (23 Refs)

77. ENERGY METABOLISM IN THE LIVER OF TUMOR-BEARING MICE.

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Soobsch Aka Nauk Gruz SSR; 104(1):197-200 1981

The effect of tumor growth on liver metabolism was studied in C3H female mice bearing mammary gland carcinoma. Progressive tumor development was associated with marked decrease of glycogen level in the liver. The changes in the activity of liver redox enzymes and phosphorylases showed no clear-cut correlation with the period of tumor growth. (6 Refs) (In RUS)

78. EFFECT OF NEOPLASMS ON THE CONTENT AND ACTIVITY OF ALKALINE PHOSPHATASE AND GAMMA-GLUTAMYL TRANSPEPTIDASE IN UNINVOLVED HOST TISSUES.

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Cancer Res; 42(6):2146-2151 1982

In rats carrying sc or ip neoplasms, there were striking (3-to 20-fold) rises in the gamma-glutamyl transpeptidase and alkaline phosphatase activity of several tissues. These included liver, lung, spleen, bone marrow, and circulating granulocytes but not lymphocytes. In response to mammary carcinoma 5A, for example, the gamma-glutamyl transpeptidase activity changed from 0.27 to 1.18 units/g lung and from 0.3 to 4.0 milliunits/million granulocytes; from 2.3 to 17 units and from 2.4 to 46 milliunits were the accompanying increases in alkaline phosphatase. These abnormalities in each host tissue were reversible in that 3 to 7 days after tumor resection the enzymes returned to control levels. Among the secondary factors which might have been responsible for the host tissue changes, it was possible to exclude stimulated adrenocortical secretion, tissue necrosis, and transplantation trauma. Comparisons of the effects of two mammary carcinomas, a fibrosarcoma, and two hepatomas on the gamma-glutamyl transpeptidase and alkaline phosphatase of various 'noninvolved' tissues indicate that the faster the growth rate of the tumors, the more striking is this host syndrome. (Author abstract) (18 Refs)

79. GLYCOSAMINOGLYCAN SYNTHESIS BY SUBPOPULATIONS OF EPITHELIAL CELLS FROM A MAMMARY ADENOCARCINOMA.

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Cancer Res; 42(6):2207-2210 1982

Glycosaminoglycan synthesis by two subpopulations of a mouse mammary tumor cell line was compared. The two sublines express distinctly different growth characteristics in vitro and in vivo which indicate differences in growth regulation. Newly made glycosaminoglycans were recovered from the culture media, the cell surfaces, and residual cellular material. The cell population which grows more aggressively in vivo (+SA subline, a subline that grows in soft agarose) incorporated about 8x more [14C]glucosamine per cell into total glycosaminoglycans than did the slower-growing population (-SA subline, which does not grow in soft agarose). Appropriate control experiments indicated that the apparent difference in rates of synthesis was not due to discrepancies in glucosamine uptake. The main residual cellular molecule labeled was heparan sulfate, but the predominant molecule at the cell surface and in the culture fluid was hyaluronic acid. Overall, +SA cells synthesized more hyaluronic acid and -SA cells synthesized more heparan sulfate; in both cell populations, these two molecules accounted for about 90% of total glycosaminoglycans produced. (Author abstract) (36 Refs)

80. NEW POSSIBILITIES FOR FAST INTRACELLULAR PH DETERMINATION IN SINGLE TUMOR CELLS BY FLOW-CYTOMETRY (MEETING ABSTRACT)

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VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Tumors frequently have a tendency for anaerobic metabolism with a lowered intracellular pH. We have developed a new method for fast intracellular pH determination in single cells using the fluorescent dye 2,3-dicyano-hydroquinone. Intracellular DCH changes the color of emitted fluorescent light from blue to green in the pH range 3.5 to 8.5. The dye was excited in a one wave length excitation mode and the fluorescence was measured in the two light channels of a FLUVO-METRICELL flow cytometer simultaneously with the cell volume. The intracellular pH in human epithelial cells of cervix uteri, small and large bowel, stomach, lung and mammary gland is initially around pH 6-6.5. It increases on differentiation to pH 6.9-7.2. The intracellular pH in human spleen, rat and guinea pig bone marrow and macrophages, human lympho- and granulocytes in contrast, is close to pH 7.2. Cancer cells at their primary location were only marginally more acidic than the normal epithelium. Cancer cells in lymph node metastases or in lung or peritoneal effusions mostly showed an intracellular pH around pH 7.2. On incubation with 40 mM glucose the inflammatory cells as lymph- and granulocytes maintained their intracellular pH while most of the tumor cells became acidic. (1 Ref)

81. RELATIONSHIP BETWEEN HISTOLOGICAL STRUCTURE AND LACTATE DEHYDROGENASE (LDH) ISOENZYME PATTERN OF INDUCED RAT MAMMARY TUMOURS (MEETING ABSTRACT)

Hullan L, Toth J, Gaal D, Holczinger L
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VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Total activity and isoenzyme pattern of LDH in mammary tumors of CFY outbred female rats induced by DMBH were studied. According to previous investigations the induced non-secreting tumors corresponded to carcinomas while only 30 per cent of the secreting ones could be regarded after a longer period of maintenance as malignant tumors. In addition to data of qualitative and quantitative histochemical and morphological studies LDH activity and isoenzyme pattern may be important markers in the biological characterization of secreting and nonsecreting tumors. In the non-secreting tumors higher LDH activity and a shift in the isoenzyme pattern, ie in the ratio of M and H subunits in favor of the M, were observed. By contrast, with the secreting tumors both enzyme activity values and ratio of subunits were more similar to the controls. Present biochemical studies suggest that the induced, non-secreting epithelial tumors of the rat mammary glands correspond to carcinoma and the secreting ones to adenoma. (no Refs)

82. FIBRONECTIN DISTRIBUTION PATTERN IN SOLID HUMAN TUMOURS (MEETING ABSTRACT)

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VI Meeting of the European Association for Cancer Research, October 12-15, 1981, Budapest, Hungary. The European Association for Cancer Research 275 pp., 1981.

Fibronectin, a structural glycoprotein, present on cell membranes and in the intercellular matrix has been reported to be lost in numerous transformed cells in cultures. Using indirect immunofluorescence, its distribution pattern has been studied in a variety of solid human tumors and corresponding normal tissues. Fibronectin could be detected on normal epithelial cell membranes, in periglandular and perivascular basement membranes and in the intercellular stroma. No modification of this distribution pattern was detected in a variety of benign tumors or in certain pathological, non-malignant disorders. In infiltrating mammary carcinomas, cell membrane staining disappeared even before invasion. The staining pattern of the glandular basement membranes became patchy, discontinuous and finally disappeared with invasion. Similar modified fibronectin patterns were observed in bronchial, endometrial, prostatic, urinary bladder and thyroid carcinomas. In sarcomas, fibronectin disappeared from the membranes of transformed cells and decreased in intensity in the intercellular matrix. (no Refs)

83. CYTOPHOTOMETRIC INVESTIGATION ON DNA IN HUMAN BREAST CARCINOMAS (MEETING ABSTRACT)

Dobreva PV, Draganov IV, Enchev VG
No affiliation given
Tenth European Congress of Cytology, October 5-7, 1981, Athens, Greece. European Federation of Cytology Societies 79 pp., 1981.

In order to provide further information on the heterogeneity of epithelial cell population in human breast carcinomas, DNA determinations were carried out on smears and paraffin sections from various breast cancers, using the single wave length of 550 nm and the plug method of Swift and Rasch. DNA values in adenocarcinomas, observed on smears and paraffin sections, were hyperdiploid-to-hypertetraploid, whereas DNA content on smears and paraffin sections from scirrhous cancer was near-diploid-to-tetraploid. Distribution of DNA values on smears from intraductal carcinoma was hyperdiploid-to-sextaploid. DNA values in squamous cell carcinoma, obtained on smears, were in triploid-to-pentaploid range, whereas DNA distribution pattern, observed on paraffin sections from undifferentiated carcinoma, was diploid-to-tetraploid. Statistical treatment indicated that differences in DNA values, obtained by measurements on smears and paraffin sections from various human breast carcinomas, were not significant. There was no direct correlation between DNA content and histological pattern of studied breast cancers. (no Refs)

84. CHARACTERIZATION OF ABNORMALITIES IN DNA CONTENT OF HUMAN SOLID TUMORS (MEETING ABSTRACT)

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Proc Am Soc Clin Oncol; 1:C-25 1982

DNA ploidy index was estimated by flow cytometry in surgical samples of 242 human solid tumors. Cell suspensions were obtained by mechanical disaggregation and stained by DNA fluorochrome 4'-6-diamidino-2-phenylindole (DAPI) without fixation in the presence of detergent. Blood leukocytes were used as a diploid standard. In 74 tumors (31%) only diploid cells were observed (DNA index 1.0). In 160 tumors one aneuploid clone was found and only 8 tumors (6 colon and 2 lung) were characterized by the presence of two aneuploid clones. Two tumors had hypodiploid DNA content. Number of tumors with aneuploid cells in relation to total number of tumors investigated was: 46/60 lung cancer (primary and metastatic), 19/27 colorectal carcinoma, 18/25 breast carcinoma, 13/21 ovarian carcinoma, 18/24 renal carcinoma, 8/14 bladder carcinoma, 4/8 prostate carcinoma, 27/37 melanoma and 15/26 sarcoma. There was continuous distribution of DNA index from 1.08 to 2.9 with apparent clusters around 1.24, 1.65, 1.96 and 2.30. The existence of clustering was supported by a one-dimensional cluster analysis using the technique of Fisher. The largest group of aneuploid tumors (54%) had a median DNA value of 1.65 and ranged from 1.45 to 1.81. DNA ploidy indexes measured in the same tumor using DNA fluorochromes with different mechanisms of binding (DAPI or propidium iodide) were highly correlated (0.97). Values of DNA-index of tumors studied may be divided arbitrarily in 5 main groups: diploid, hyperdiploid, hypertriploid, tetraploid and hypertraploid. (1 Ref)

85. MEMBRANE MICROVISCOSITY INCREASES IN REGRESSING NITROSOMETHYLUREA (NMU) INDUCED MAMMARY CARCINOMA (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:938 1982

The objective of these studies was to determine if the changes observed in prolactin-binding capacity of membranes from growing and regressing NMU induced mammary carcinoma correlated with those observed in membrane microviscosity measurements. Buffalo female rats were intravenously injected with 5 mg/100 g body weight of NMU at 50, 80 and 110 days of age. Mammary tumors induced in Buffalo rats by treatment with NMU are known to regress after oophorectomy. These rats were, therefore, either sham operated or oophorectomized at 5 months of age and sacrificed at 1, 3, 4, 5 and 8 days after the surgery. The 100,000 x g membrane pellets of these growing or regressing tumors were used for oPRL binding and fluidity studies. Membrane microviscosity was studied by fluorescence polarization at 24 C using a lipid probe 1,6 diphenylhexatriene (1 uM in PBS at pH 7.1). A 46% decrease in prolactin-binding capacity was observed in membranes obtained from animals sacrificed 8 days after oophorectomy. Such a decrease in prolactin binding capacity of membranes from regressing tumors is well documented. Fluorescence polarization values were low in membranes from growing tumors which increased progressively with time after oophorectomy, reaching a maximal value at 5 days after oophorectomy, the values being 0.140, 0.188, 0.226, 0.227, 0.248 and 0.250, for membranes from growing tumors and 1, 3, 4, 5 and 8 days regressing tumors, respectively. A similar difference in membrane fluorescence polarization values was observed in growing and regressing DMBA-induced mammary carcinoma. (no Refs)

86. PROPERTIES AND CHARACTERISTICS OF ADENYLATE CYCLASE IN NORMAL AND FIBROCYSTIC BREAST EPITHELIAL CELLS IN HUMANS (MEETING ABSTRACT)

Foecking MK, Abou-Issa H, Minton JP
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Fed Proc; 41(3):1409 1982

Basal, fluoride and hormone-stimulated activities of adenylate cyclase (AC) have been studied in mammary epithelial cells of human tissues freed from adipose tissue. Epithelial cells were isolated by collagenase treatment of normal and fibrocystic breast tissues. The apparent Km for MgATP2-in both tissues is 1.0x10(-4) M. AC in both tissues is stimulated only by catecholamines and prostaglandins (PGE1, PGE2). The enzyme was maximally activated (2 x basal activity) by L-epinephrine (EPI) with an apparent Km of 2.0 x 10(-6) M. Norepinephrine also stimulated the activity but with an increased apparent Km of 8 x 10(-5) M. PGE1 and PGE2 (at 10(-6) M) stimulated the basal activity of AC by 140% and 95% respectively. EPI and PGE1 together have no additive stimulatory effect indicating separate receptor sites for each hormone. The stimulation by EPI or PGE1 is potentiated 4-and 2.5-fold respectively by the addition of 10 x 10(-5) M Gpp (NH)p. The apparent Km for Gpp(NH)p is approximately 15 uM. The catecholamine stimulation appears to be mediated through Beta 2 adreno-receptors. AC from fibrocystic breast has an increased responsiveness to EPI compared to normal tissue both in the absence and presence of Gpp(NH)p. However no difference was observed in PGE1-responsiveness in both tissues. The results suggest increased catecholamine responsiveness play a developmental role in fibrocystic breast disease. (no Refs)

87. CORRELATION OF THYMIDINE KINASE ACTIVITY, HISTOLOGY AND STEROID RECEPTORS IN PRIMARY BREAST CANCER (MEETING ABSTRACT)

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Proc Am Soc Clin Oncol; 1:C-29 1982

Tumor steroid receptor content and differentiation correlate with the recurrence rate of primary breast cancer. For predicting prognosis, we investigated another biological marker, thymidine kinase activity (TK) by the method of Breitman, as well as estrogen receptor (ER) by the DCC method and progesterone receptor (PgR) by the sucrose gradient method. Results were correlated in 48 primary breast cancer tissues. No correlation was found between TK and PgR in 38 tumors. When tumors were divided into ER-poor (less than 3 fmol), medium (3-30 fmol), and rich (greater than 30 fmol) groups, a correlation of TK with ER was found in the first two groups. High TK activity occurred in 71% (10/14) of ER-poor tumors, while only in 18% (3/18) of ER-medium tumors. In the ER-rich group, 9 of 16 tumors also contained high TK, probably resulting from 'hormonal stimulation.' In 33 tumors, detailed histological grade was analyzed by the method of Bloom and Richardson, and no correlation with TK was found. This study suggests that (1) ER-poor primary breast tumors usually have high TK and (2) high TK also exists in some of the ER-rich tumors. The significance of TK as a prognostic factor for disease recurrence and for response to chemotherapy warrants further study. (no Refs)

88. ESTROGEN-INSENSITIVE PROGESTERONE RECEPTORS IN A HUMAN BREAST CANCER CELL LINE: CHARACTERIZATION OF RECEPTORS AND OF A LIGAND EXCHANGE ASSAY.

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Endocrinology; 110(5):1564-1571 1982

In modified culture conditions, T47D human breast cancer cells synthesize extraordinary amounts of progesterone receptors (PgR), but, unlike other progesterone target cells, the PgR are entirely independent of estrogen controls. In the present studies we characterize some physicochemical properties of the PgR in T47D cells. We also describe an exchange assay for cytoplasmic and nuclear forms of the receptors which has enabled us to demonstrate that after progesterone treatment, translocation is stoichiometric. Despite the anomalous regulation of PgR levels, these receptors are typical of steroid receptors; they sediment at 7-8S on sucrose density gradients, they bind ligands with high affinity (Kd approx 4 nM for R5020; Kd approx 2 nM for progesterone), they bind only progestins specifically, and they are thermolabile (t1/2 at 37 c is approx 15 min). Receptor levels range from 15-40 pmol/mg DNA, or more than 300,000 sites/cell. The ability of ligands to dissociate from and rebind to the receptors was measured and used in an exchange assay for nuclear PgR. The synthetic progestin R5020 dissociates readily from receptors (t1/2 approx 3 hr at 0 C and 1.5 hr at 10 C), and the dissociation of progesterone is even faster (t1/2 approx 30 min at 0 C). To quantify steroid exchange, receptor levels were measured in mixtures of hormone-filled and unfilled cytosols. These studies assess ligand dissociation and subsequent ligand rebinding. At 0 C for 4-18 hr or at 10 C for 4 hr, unlabeled progesterone dissociates from receptors, and R5020 rebinds all sites, resulting in 100% exchange. In contrast, despite the use of a variety of incubation times and temperatures, no more than 50% of receptors previously filled with R5020 can exchange for [3H]R5020. The progesterone to [H3]R5020 exchange assay was used to measure salt-extracted nuclear progesterone receptors. In cells treated for 5 min with 0.1 uM progesterone, all depleted cytoplasmic sites were quantitatively recovered from nuclei. These cells provide a new model system to study the molecular biology of human PgR. (Author abstract) (37 Refs)

89. A STUDY OF CYTOPLASMIC OESTROGEN RECEPTORS IN PATIENTS WITH BREAST CANCER IN A DISTRICT GENERAL HOSPITAL.

Spencer GR, Prothero DL, Dawkins PD, Akehurst AC, Turner DR
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Br J Surg; 69(4):191-192 1982

The tumors of 61 patients suffering from primary adenocarcinoma of the breast were assayed for estrogen receptors (ER), using the dextran-coated charcoal method. A statistically significant relationship (p less than 0.05) was found to exist between ER status and the histological grade of the tumor. No relationship was found between ER status and either tumor size or the pathological state of the axillary lymph nodes. It is concluded that it is a practical proposition to establish an ER assay service in a district general hospital, with subsequent benefits for the individual patient. (Author abstract) (13 Refs)

90. STEROID RECEPTORS IN HUMAN BREAST CANCER TISSUE.

Brentani MM, Pacheco MM, Oshima CT, Nagai MA, Goes JC
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Rev Latinoam Oncol Clin; 13(4):22-29 1981

Steroid receptors in a group of primary breast cancer patients were analyzed. Estrogen (ER), progesterone (PR), and glucocorticoid (GR) receptors were present in 60% of 350, 59% of 288, and 61% of 233, respectively, of the cancer patients. Frequency of ER, PR, and GR positivity was approx the same in pre- and postmenopausal women, but ER content was much higher in postmenopausal women. The likelihood of positive PR in a tumor increases with increasing ER content. The mean level of PR or GR decreases in tumors that lack ER. (20 Refs)

91. CORRELATION OF EPIDERMAL GROWTH FACTOR RECEPTORS WITH ESTROGEN AND PROGESTIN RECEPTOR CONCENTRATIONS IN BREAST CANCER (MEETING ABSTRACT)

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Fed Proc; 41(3):1163 1982

Epidermal growth factor (EGF) is a mitogen for MCF-7 human breast cancer cells in vitro, suggesting a role in regulating the growth of some human breast carcinomas in vivo. Similarly, estrogen is a mitogen for ZR-75-1 human breast cancer cells in vitro and the clinical usefulness of estrogen (ER) and progestin receptors (PR) for selecting those breast cancer patients likely to respond to endocrine therapy is well established. The concentrations of EGF receptor have been measured in crude membrane pellets from each of 65 unselected primary and metastatic breast carcinomas using a single saturating level of 125I-labeled mouse EGF. The affinity (approx 10-10M) and saturation kinetics were determined separately. ER and PR were determined using 3H-labeled ligands in separate titration assays. A substantial percentage (42%) of the tumors contained significant levels of EGF receptor (1-37 fmol/mg membrane protein). Tumors with EGF receptors usually did not exhibit ER and PR and visa versa, while some tumors lacked EGF receptors as well as ER and PR. EGF receptor level was not correlated with patient age. These data suggest that EGF receptors may characterize certain human breast carcinomas which are unresponsive to endocrine therapies employed currently. (no Refs)

92. PROGESTERONE RECEPTORS IN SPONTANEOUSLY OCCURRING FELINE MAMMARY ADENOCARCINOMAS (MEETING ABSTRACT)

Johnston SD, Hayden DW, Johnson KH, Handschin B, Theologides A, Kiang DT
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Proc Am Assoc Cancer Res; 23:939 1982

Cytosol estrogen and progesterone receptor (ER, PR) concentrations were determined in spontaneously occurring mammary adenocarcinomas from seven cats. Receptor concentration was determined using sucrose gradient centrifugation following dextran-coated charcoal separation of cytosols binding radiolabeled ligand (in presence and absence of 100 X competitor) and free ligand. Binding was evaluated with and without glucocorticoid competitors in the presence of sodium molybdate. None of the cytosols contained detectable estradiol receptors; all contained 5 S progesterone receptors, with concentrations ranging from 4.0 to 11.7 fmol/mg protein. A dissociation constant of 3.47 nM was determined by Scatchard plot analysis of binding in one cytosol. While PR concentrations were lower than those found in steroid responsive human tumors, their presence in all of the tumors (from four ovariohysterectomized and three intact female cats) in the absence of ER suggests that the feline mammary adenocarcinoma may be a progesterone dependent tumor, similar to the small group of ER-, PR+ human mammary tumors. (no Refs)

93. SELECTIVE RESPONSE OF TUMORS TO MICROWAVE HYPERTHERMIA (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:870 1982

Previous studies in this laboratory used microwave hyperthermia as an adjunct to X-irradiation and misonidazole. The present study is concerned with effects induced by microwave hyperthermia alone. Two mouse mammary carcinomas (MT2, DBAH) and a spindle cell sarcoma (TEC) of standard size growing in isogeneic hosts have been exposed to 4250 MHZ induced microwave hyperthermia at 42-43 C for a predetermined time of 60 min for 5 days. Measurements of treated and control tumors were made daily. At 12-24 hrs post treatment the tumors increased slightly, presumably due to edema. Shrinkage of tumors started about 48 hrs later. Of the three types of tumors treated, the DBAH proved most thermosensitive, regressing completely within 2 to 3 weeks after treatment. The MT2 carcinoma similarly treated formed a dark crust in the center while new growth appeared at the edge of the treated tumor. Of the TEC tumors treated daily for 60 min seventy-five percent totally regressed, the remainder continued to grow at a slower rate. The results indicate a difference in thermoresponse among the three tumor types and emphasize the significance of studying each tumor type individually. The mechanism(s) of microwave effects on cellular components is being studied by high pressure liquid chromatography. (1 Ref)

94. EFFECT OF CYTOTOXIC DRUGS ON ESTROGEN RECEPTOR LEVEL OF HUMAN BREAST CANCER CELLS (MCF-7) (MEETING ABSTRACT)

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Proc Am Assoc Cancer Res; 23:940 1982

Effect of cytotoxic drugs on estrogen receptor (ER) content of human breast cancer was investigated on an extensively-used model for ER-positive human breast cancer, MCF-7 cell line. MCF-7 cells, growing in the log phase, were incubated in serum- and hormone-free medium with 10(-6)-10(-4) M methotrexate (MTX), 5-fluorouracil (5-FU), or vincristine (VCR) at 37 C for 3 hours. 3H-estradiol (3H-E2) was then added and the cells were incubated at 37 C for an additional hour. In addition to 3H-E2, duplicates received 200-fold excess radioinert diethylstilbestrol to determine nonspecifically bound 3H-E2. The intracellular specific binding of 3H-E2 to MCF-7 cells was measured by the method of Shafei and Brooks. Treatments of MCF-7 with MTX, 5-FU, or VCR resulted in a 25-64% reduction of 3H-E2 specific binding; and the reduction was dose-related. When MTX and 5-FU were administered in combination (1 x 10(-5) M each) to the cells, there was a synergistic decrease of ER level. Nuclear uptake of 3H-E2 in drug-treated

MCF-7 was also significantly reduced (55-68% of control). Scatchard plot analysis reveals a reduction of receptor number with no change on binding affinity in the drug-treated cells. (1 Ref)

95. GENETIC DISTINCTION BETWEEN NEOPLASTIC GROWTH OF MAMMARY EPITHELIUM AND GROWTH IN 'TUMOR STEM CELL' ASSAYS (MEETING ABSTRACT)

Stanley WS, Montgomery J, Soule HD, McGrath CM
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Proc Am Assoc Cancer Res; 23:914 1982

Growth of solid tumor cells in agar or methylcellulose (MC) suspension is commonly used as a selective indicator for behavior of tumor 'stem cells'. The use of suspension cultures in 'stem cell assays' implies that controls for tumorigenic growth and growth in suspension are identical or very similar. We brought this idea in mammary cancer into question by demonstrating 1) that mammary cells cloned in MC failed to grow as tumors; and 2) tumorigenic cells cloned on solid substrates failed to grow in MC. We approached the problem further using somatic cell genetics. We found that the tumorigenic phenotype of a mouse mammary cell line (66CL) was expressed as a recessive trait (ie was suppressed) in intraspecies hybrids formed with normal lymphocytes and mammary cells. Fusions of 66CL cells with other tumorigenic cells gave evidence that the recessive lesions were allelic and that suppression of tumorigenicity was not due to host/cell incompatability factors. Hybrid clones suppressed for tumorigenicity nonetheless readily formed colonies in MC. Thus growth in MC was dominantly expressed and not coordinately suppressed with tumorigenicity. No hybrid clones exhibited a hyperplastic or precancerous phenotype. These data suggest that the genetic controls governing tumorigenicity in different tumor cells is the same but separate from controls governing growth in MC. Thus, growth in MC is not likely to be a selective condition for tumorigenic mammary 'stem cells'. Expression of tumorigenicity as a recessive trait is compatible with the two-step theory of transformation, though acquired ability to grow in MC suspension does not coincide with either precancerous or cancerous transformation. (no Refs)

96. HETEROGENEITY OF THE HUMAN BREAST CANCER CELL LINE MCF-7 (MEETING ABSTRACT)

Butler WB, Berlinski PJ, Kelsey WH, Toenniges MM
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:931 1982

MCF-7 is an uncloned cell line which has been reported to contain cells of different morphologic phenotypes. We have isolated several clones of MCF-7 cells and five of them were used in these studies. The clones differ in morphology when grown in vitro with their appearance being partially dependent on the growth medium. All five contain estrogen receptor, as does the parent culture, and the growth of all five in culture is inhibited by the antiestrogen tamoxifen. Using female BALB/c (nu/nu) mice we found, as have others, that our parent MCF-7 cells formed progressively growing tumors only when the mice were given supplemental estrogen in the form of 1 cm implants of silastic tubing filled with estradiol. Of the five MCF-7 clones tested, only two produced tumors which grew progressively in nude mice. Like the parent cells, both clones required estrogen supplementation for tumor growth. Preliminary experiments have shown no evidence that, for these five clones, there is a correlation between the ability to form colonies in soft agar and tumorigenicity. Further study of the in vitro characteristics of these and other clones of MCF-7 should provide information on the properties of human breast cancer cells which do correlate with tumorigenicity and on the role of estrogen in stimulating tumor growth. (1 Ref)

97. INCREASED ACTIVITY OF A BETA-GALACTOSYLTRANSFERASE IN TISSUES OF RATS BEARING PROSTATE AND MAMMARY ADENOCARCINOMAS.

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Cancer Biochem Biophys; 6(1):37-45 1982

The levels of UDP-galactose:N-acetylglucosamine(beta1 4)galactosyltransferase activity (GalT-4) were determined in the sera, in solid tumors, and in corresponding cell cultures of rats bearing two lines of prostate adenocarcinomas (PA-2 and PA-3) and in the sera of rats bearing other transplanted and autochthonous adenocarcinomas. Sera and tissues from normal (tumor-free) rats were used as controls. Prostate adenocarcinoma cell cultures had 5x greater levels of enzyme activity than did tumor cell infiltrated lymph nodes from animals bearing the prostate adenocarcinomas. The levels of activity in the cells of both prostate tumor lines were equivalent, even though they metastasize through different routes. Serum levels of galactosyltransferase activity were elevated only in animals with prostate tumor line PA-2, in which tumor cells were detected in the blood, and in rats bearing a mammary adenocarcinoma with extensive necrosis of the tumor mass (tumor mass greater than 22.0 g/200 g body wt). The increase was 3x the control value. The sera of L-W rats bearing prostate tumors (PA-2 and PA-3) were inactive with the GalNAc-containing acceptor, GM2 (GalNAcbeta1-4(NeuAcalpha2-3)Galbeta1-4Glc-Cer), but active with either free GlcNAc (Km = 0.25 mM) or LcOse3Cer (GlcNAcbeta1-3Galbeta1-4Glc-Cer; GlcNAc-R). (Author abstract) (38 Refs)

98. CYTOCHEMICAL STUDY OF RNA IN CELLS OF ANTERIOR PITUITARY GLAND OF RATS WITH 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) INDUCED MAMMARY GLAND CARCINOMA.

Ganina KP, Iareshko AG

Inst. Problems Oncology, Kiev, USSR

Tsitol Genet; 16(1):3-6 1982

The functional activity of the anterior pituitary gland (APG) was studied in albino female rats subjected to iv administration of 7,12-dimethylbenz(a)anthracene (DMBA: 2 mg/day). Animals were sacrificed on days 10 and 40 after the termination of DMBA administration, and after the appearance of first palpable tumors of the mammary glands. Cytomorphological examination of the APG showed enhanced vascularization, progressive increase of the number of basophilic cells, and significant decrease of the number of acidophilic cells. The RNA content in the cytoplasm of basophilic cells showed decrease (from 1.51 units in controls, to 1.40 on day 10, 1.47 on day 40, and and 1.33 in tumor-bearing animals). RNA content in the nucleoli of basophilic cells was 1.01, 0.78, 0.87, and 0.76 units, respectively. Development of mammary gland tumors was associated with increase of RNA content in the cytoplasm and nucleoli of acidophilic cells. (13 Refs) (In RUS)

99. STEROID HORMONE RECEPTORS AND SEX CHROMATIN FREQUENCY IN BREAST CANCER.

Smethurst M, Bishun NP, Fernandez D, Allen J, Burn JI, Alaghband-Zadeh J, Williams DC
Res. Dept., Marie Curie Memorial Foundation, The Chart, Oxted, Surrey RH8 OTL, England
J Endocrinol Invest; 4(4):455-457 1981

Seventeen primary breast tumors were divided into three groups according to the frequency of sex chromatin and subdivided according to the presence or absence of steroid receptors. Of the cytosol estrogen receptor positive tumors, only 3/15 showed a sex chromatin frequency of less than 10%. Of the tumors with frequencies of 11-20% or greater than 20%, 7/7 had estrogen and progesterone receptors, 6/7 had cytosol and nuclear estrogen receptors, and 6/7 had all three receptors. A possible association between the presence of steroid hormone receptors and sex chromatin frequencies of greater than 20% is suggested. (12 Refs)

100. SALIVARY NITRITES IN PHYSIOLOGICAL AND VARIOUS PATHOLOGICAL CONDITIONS INCLUDING CANCER.

Bhide SV, D'Souza AV, Shivapurkar NM, Patel DN, Shetty PA
Carcinogenesis Div., Cancer Res. Inst., Parel, Bombay 44 012, India
Indian J Cancer; 19(1):7-10 1982

Salivary nitrites were studied in human cancers of various sites (tongue, maxilla, breast, ovary) as well as in leukemia. Also included in the study were patients with leukoplakia in the oral mucosa (possibly preneoplastic) and those with simple dental problems. All oral cancer patients had low nitrite values but 80% of breast cancer cases and 60-70% of other cancer types also showed low values. The majority of pregnant women or patients with dental disorders did not show low nitrite values. Since the Indian diet is rich in nitrite-containing vegetables, a significant postprandial increase in salivary nitrites occurred in pregnancy, normal subjects and individuals with malignancies other than oral cancer. Patients with oral cancer did not show a postprandial increase, possibly indicating damaged oral mucosa rather than poor food intake. (9 Refs)

101. RETINOIC ACID BINDING PROTEINS AND STEROID RECEPTOR LEVELS IN HUMAN BREAST CANCER.

Mehta RG, Kute TE, Hopkins M, Moon RC
Life Sciences Div., IIT Res. Inst., 10 West 35th St., Chicago, IL, 60616
Eur J Cancer Clin Oncol; 18(3):221-226 1982

Samples of 31 human breast cancer tissues were examined for the presence or absence of cytosolic retinoic acid binding proteins (cRABP), estrogen receptors (ER) and progesterone receptors (PR). cRABP were detected as specifically sedimenting 2S components on sucrose density gradients. Specific binding under the 2S region for cRABP and under the 8S region for ER and PR were determined. The levels of cRABP ranged from less than 1 pmol to 14 pmol per mg of cytosol protein. Tumors containing less than 3 pmol cRABP were designated as low cRABP; tissues were considered ER- and PR- when the receptor levels were less than 10 fmol/mg protein. Approx 60% of primary and metastatic tumors examined contained high cRABP. Tumors with well differentiated histopathology exhibited increased levels of cRABP. There was no significant correlation between the presence or absence of steroid receptors and cRABP in human mammary tumors. (Author abstract) (25 Refs)

REVIEWS AND OTHER RELATED STUDIES

102. CANCER - PRINCIPLES AND PRACTICE OF ONCOLOGY.

DeVita VT, Hellman S, Rosenberg SA
NCI, Bethesda, MD
Cancer - Principles and Practice of Oncology. Philadelphia, Lippincott, 1926 pp., 1982.

Principles and practices in oncology are reviewed with the aim of presenting an integrated multidisciplinary approach to cancer. Principles of oncology are presented with respect to the cause and evolution of cancer as a biologic phenomenon. The essential principles of modern cancer diagnosis and treatment are discussed, and topics include epidemiology; etiology and prevention of cancer; cell biology and biochemistry; kinetics of cellular proliferation; biology of cancer metastasis; principles of surgical oncology, chemotherapy, and radiotherapy; clinical pharmacology of cancer chemotherapy; design and conduct of clinical trials; diagnosis and staging; and psychosocial aspects of patients with cancer. Practice of Oncology is presented with respect to the management of specific cancers and complications caused by either the cancer itself or its treatment. Topics include cancer of the head and neck, stomach, lung, mediastinum, esophagus, pancreas, hepatobiliary system, small intestine, colon and rectum, anal region, genitourinary system, testis, ovary and other gynecologic organs, breast, endocrine system, and skin; sarcomas; cutaneous and intraocular melanomas; tumors of the CNS; childhood cancers; Hodgkin's disease; non-Hodgkin's lymphomas; adult acute leukemias; chronic leukemias; plasma cell neoplasms; paraneoplastic syndromes; management of the patient with an unknown primary site; treatment of metastatic cancer; oncologic emergencies; supportive care; infections; adverse effects of treatment; rehabilitation; administration of cancer treatments; newer methods of cancer treatment; and unproven methods of cancer treatment. (11312 Refs)

103. CANCER OF THE BREAST.

Hellman S, Harris JR, Canellos GP, Fisher B
Dept. Radiation Therapy, Harvard Medical Sch., Boston, MA
Cancer - Principles and Practice of Oncology. DeVita VT, Hellman S, and Rosenberg SA, ed. Philadelphia, Lippincott, 1926 pp., 1982.

Epidemiology, pathology, classification of tumor types, tumor characteristics, local and regional spread, staging, theories on the spread, pretreatment evaluation, screening, and treatment of breast cancer are reviewed. Conservative surgery and/or radiotherapy (RT) and radical mastectomy (with or without RT) are about equally effective local treatments. Treatment of Stage III disease requires a combination of effective local treatment (usually RT) and systemic therapy. Menstrual status, extent of disease, and the tumor's estrogen receptor (ER) content should be used to select candidates for endocrine therapy (additive or ablative), antiestrogen, and chemotherapy. Combinations of cyclophosphamide with 5-fluorouracil and methotrexate or adriamycin are the most effective cytotoxic regimens. Patients with extensive, rapidly progressive metastases seldom respond to endocrine therapy and should be given chemotherapy. In other cases, the sequence of administration of endocrine therapy and chemotherapy is unrelated to survival. Endocrine therapy may be effective in patients with ER-positive tumors who relapse after chemotherapy, but second-line chemotherapy tends to be ineffective. Sequential administration of alternating non-cross-resistant cytotoxic regimens does not improve the occurrence or duration of remissions. Recurrences may consist of cross-resistant cell lines. A combination of vinblastine and mitomycin C may be useful against these refractory relapses. Further progress in therapeutic research will require continuing admission of patients to clinical trials. Since systemic therapy is palliative in most patients with advanced disease, potentially effective new treatments may be given to patients in symptomatic early relapse from the best first-line chemotherapy. Diagnosis and treatment of lobular breast cancer in situ and of breast cancer in males are discussed. (396 Refs)

104. FUTURE DEVELOPMENTS IN RESEARCH WITH RELEVANCE TO HUMAN BREAST CANCER.

Neville AM
Ludwig Inst. for Cancer Res., Royal Marsden Hosp., Sutton, Surrey SM2 5PX, England

Breast Cancer Management: The Experience of the Combined Breast Clinic, St. George's Hospital/The Royal Marsden Hospital. Coombes RC, Powles TJ, Ford HT, and Gazet JC, ed. London, Academic Press, 317 pp., 1981.

Possible areas of future developments in research with relevance to human breast cancer are discussed, including aspects of etiology, detection of metastatic disease, and biology of the breast and its tumors. Breast disease should not be viewed in a conventional endocrine sense. Factors which are involved intimately in the control of breast cell growth, both normal and neoplastic, should be examined. An understanding of such factors will allow better insight into the progression of breast cancer and how it may be modulated to the patient's advantage. (35 Refs)

☆ U. S. GOVERNMENT PRINTING OFFICE : 1982—361-847/126

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. MICROWAVE HEATING ENHANCES THE MIGRATION OF PLASTICIZERS OUT OF PLASTICS.
Bishop CS, Dye A
East Tennessee State Univ., Johnson City, TN, 37614
J Environ Health; 44(5):231-235 1982

2. DISEASES CAUSED BY EPOXY RESINS.
Konietzko H, Fischer G
Institut fur Arbeits- und Sozialmedizin, Johannes-Gutenberg-Universitat, Obere Zahlbacher Strasse 67, D-6500 Mainz, W. Germany
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3. NITROSAMINES.
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Pneumonologische Abteilung, Krankenhaus der Elisabethinen, Fadingerstr. 1, A-4020 Linz-Donau, Austria
Wien Med Wochenschr; 132(71,Suppl):75-79 1982
In GER

4. EXPERIMENTAL TUMORS OF THE PERIPHERAL NERVOUS SYSTEM.
Beniashvili DS
Cancer Res. Center, Tbilisi, USSR
Eksp Onkol; 4(2):12-19 1982
In RUS

5. MUTAGENIC, CARCINOGENIC AND TERATOGENIC EFFECTS OF STYRENE.
Sram RJ, Pohlova H, Topinkova E
Klinika hygieny a epidemiologie, Srobarova 48, 100 42 Prague 10, Czechoslovakia
Prac Lek; 34(2):68-72 1982
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6. DIETHYLSTILBESTROL: EFFECT OF IN UTERO EXPOSURE.
Burke L
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Curr Probl Obstet Gynecol; 5(2):1-58 1981

7. IN UTERO EXPOSURE TO DIETHYLSTILBESTROL: ADVERSE EFFECTS ON THE REPRODUCTIVE TRACT AND REPRODUCTIVE PERFORMANCE IN MALE AND FEMALE OFFSPRING.
Stillman RJ
Dept. Obstetrics and Gynecology, George Washington Univ. Sch. Medicine and Health Sciences, 2150 Pennsylvania Ave., NW, Washington, DC, 20037
Am J Obstet Gynecol; 142(7):905-921 1982

8. BIOLOGICAL EFFECTS OF MINERAL WOOL.
Petersen R, Ehrhorn H, Mousing K, Sabroe S, Silberschmid M, Venstrup-Nielsen SE
Socialmedicinsk institut, Vesterbro Torv 1-3, DK-8000 Arhus C, Denmark
Ugeskr Laeger; 144(13):971-975 1982
In DAN

DIETARY FACTORS IN CARCINOGENESIS

9. NATURALLY OCCURRING FOOD TOXICANTS: PHENOLIC SUBSTANCES OF PLANT ORIGIN COMMON IN FOODS.
Singleton VL
Dept. Viticulture and Enology, Univ. California, Davis, CA
Adv Food Res; 27:149-242 1981

10. MUTAGENS, CARCINOGENS, AND TUMOR PROMOTERS IN OUR DAILY FOOD.
Sugimura T
Natl. Cancer Res. Inst., Tsukiji, Chuo-ku, Tokyo, Japan
Cancer; 49(10):1970-1984 1982

11. THE BIOLOGICAL EFFECTS OF CARRAGEENAN AND OTHER SULFATED POLYSACCHARIDES WITH PARTICULAR ATTENTION TO IMMUNOLOGICAL AND CARCINOGENIC PROPERTIES.
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12. VARIATIONS AMONG SPECIES AND CELL TYPES IN THE EFFECTS OF CAFFEINE ON MUTAGEN-INDUCED CYTOTOXICITY AND POSTREPLICATION REPAIR OF DNA.
Sivak A, Rudenko L, Teague LG
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Prev Med; 11(2):232-239 1982

14. MEASUREMENT OF CANCER INCIDENCE IN THE UNITED STATES: SOURCES AND USES OF DATA.
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16. CURRENT CONCEPTS OF THE ETIOLOGY AND PATHOGENESIS OF LUNG CANCER.
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19. PREDICTIVE IDENTIFICATION OF HYPERSUSCEPTIBLE INDIVIDUALS.
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Dept. Environmental Health, Univ. Washington, Seattle, WA, 98195
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ENVIRONMENTAL AND OCCUPATIONAL FACTORS IN CARCINOGENESIS

21. POLYCHLORINATED BIPHENYLS (PCBS): AN AUSTRALIAN VIEWPOINT ON A GLOBAL PROBLEM.
Richardson BJ, Waid JS
Marine Science Lab., Ministry for Conservation - Victoria, P.O. Box 114, Queenscliff, Victoria 3225, Australia
Search; 13(1/2):17-25 1982

22. SIGNIFICANCE OF ENVIRONMENTAL FACTORS FOR THE DEVELOPMENT OF LEUKEMIA, MYELOMA AND MALIGNANT LYMPHOMA.
Brandt L
Onkologiska kliniken, Lasarettet, Lund, Sweden
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23. ENVIRONMENTAL FACTORS AND MALIGNANT HEMATOLOGICAL DISEASES.
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Hemataologsektionen, Danderyds sjukhus, Danderyd, Sweden
Lakartidningen; 79(15):1457-1459 1982
In SWE

CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS

24. REGULATION OF GENE EXPRESSION IN NORMAL AND NEOPLASTIC CELLS. A REVIEW.
Hochhauser SJ, Stein GS, Stein JL
Dept. Biochemistry and Molecular Biology, Univ. Florida, Coll. Medicine, Gainsville, FL, 32610
Pathobiol Annu; 11:1-29 1981

25. WHAT ARE ISOZYMES TELLING US ABOUT GENE REGULATION IN CANCER?
Weinhouse S
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JNCI; 68(3):343-349 1982

26. CHANGES IN AMINO ACID AND SUGAR TRANSPORT ACTIVITY ASSOCIATED WITH MALIGNANT TRANSFORMATION.
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Dept. Biochemistry, Kyoto Prefectural Medical Univ., Kyoto, Japan
Tanpakushitsu Kakusan Koso; 26(7):881-895 1981
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27. CURRENT VIEWS ON THE NATURE OF MYOEPITHELIAL CELLS AND THEIR ROLE IN THE MORPHOGENESIS OF DYSHORMONAL HYPERPLASIAS AND BREAST TUMORS.
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Central Lab. Pathology, Inst. Human Morphology, Moscow, USSR
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28. OVERVIEW: RETINOIDS AND CARCINOGENESIS.
Schramm T, Coutelle R
Zentralinstitut fur Krebsforschung, Akademie der Wissenschaften der DDR, Lindenberger Weg 80, DDR-1115 Berlin-Buch, E. Germany
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Lower GM, Kanarek MS
Dept. Veterinary Science, Coll. Agricultural and Life Sciences, Univ. Wisconsin, 1655 Linden Drive, Madison, WI, 53706
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30. THE ANTITUMOR POLYSACCHARIDE LENTINAN: AN OVERVIEW.
Chihara G
Natl. Cancer Res. Inst., Tsukiji, Tokyo, Japan
Excerpta Med Int Congr Ser; 576:1-16 1981

VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

31. ENDOGENOUS ONCOGENIC TYPE B VIRUSES IN MICE.
Komarova EA, Kriukova IN
All-Union Cancer Res. Center, Moscow, USSR
Eksp Onkol; 4(2):3-12 1982
In RUS

32. GENETIC INTERACTIONS BETWEEN TUMOR VIRUSES AND HOST CELLS.
Rowe WP
Lab. Viral Diseases, Natl. Inst. Allergy and Infectious Diseases, NIH, Bethesda, MD, 20205
Cancer; 49(10):1958-1962 1982

33. THE PERSISTENCE OF RETROVIRUSES.
Weiss RA
Chester Beatty Res. Inst., Fulham Road, London SW3 6JB, England
Symp Soc Gen Microbiol; 33:267-288 1982

34. HOW DO PAPOVA VIRUSES PERSIST IN THEIR HOSTS?
Griffin BE
Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Symp Soc Gen Microbiol; 33:227-247 1982

35. THE EPSTEIN-BARR VIRUS: HISTORICAL, BIOLOGIC, PATHOLOGIC AND ONCOLOGIC CONSIDERATIONS.
Seemayer TA, Oligny LL, Gartner JG
Dept. Pathology, Montreal Children's Hosp., Montreal, Quebec, Canada
Perspect Pediatr Pathol; 6:1-33 1981

36. KAPOSI'S SARCOMA: WHY A 'HOMOSEXUAL DISEASE'?
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Div. Hematology-Oncology, Univ. California at Los Angeles Sch. Medicine, Los Angeles, CA
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METHODOLOGY IN CARCINOGENESIS RESEARCH

37. MAJOR APPROACHES TO THE EXPERIMENTAL STUDY OF LUNG CANCER.
Pliss GB, Turusov VS, Zabezhinskii MA
No affiliation given
Vopr Onkol; 28(2):18-22 1982
In RUS

38. ON THE NECESSITY OF MUTAGENICITY TESTING OF NEW DRUGS.
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Zaklad Genetyki Czlowieka, PAN, 60-479 Poznan, Poland
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OTHER REVIEWS IN CARCINOGENESIS

39. CANCER - PRINCIPLES AND PRACTICE OF ONCOLOGY.
DeVita VT, Hellman S, Rosenberg SA

NCI, Bethesda, MD
Cancer - Principles and Practice of Oncology. Philadelphia, Lippincott, 1926 pp., 1982.

40. MOVABLE GENETIC ELEMENTS.

Watson JD

Cold Spring Harbor Lab., Box 100, Cold Spring Harbor, NY, 11724

Cold Spring Harbor Symp Quant Biol 45(part 1): 445 pp., 1981.

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OCTOBER, 1982

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EPIDEMIOLOGY OF BREAST CANCER IN HUMAN POPULATIONS

1. CANCER OF THE BREAST IN BALTIMORE BLACK WOMEN.

Miller JM, Kong BW

Provident Hosp., Inc., 2600 Liberty Heights Ave., Baltimore, MD, 21215

Md State Med J; 31(5):52-53 1982

The leading cause of death from malignancy in white women (WW) is breast cancer and the incidence is generally higher in more affluent socioeconomic groups. In Baltimore, the age adjusted mortality rates for WW changed little in the period 1970-1979 but in black women (BW) an increase was found in age adjusted death rate (22.28 WW vs 31.33 BW in 1979). This higher death rate in BW is paradoxically associated with a lower socioeconomic level which may be due to limited access to medical treatment. (17 Refs)

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2. TEMPORAL TRENDS IN BREAST CANCER.

Stevens RG, Moolgavkar SH, Lee JA
Inst. Cancer Res., 7701 Burholme Ave., Philadelphia, PA, 19111
Am J Epidemiol; 115(5):759-777 1982

Time-depth breast cancer mortality data from the United States, England and Wales, Canada, and Japan, and breast cancer incidence data from Connecticut, Denmark, and Osaka, Japan, were analyzed. The temporal trends in mortality have been similar in the populations examined. Risks for individual cohorts decreased until about the cohort of 1900, when they began to increase. This pattern can account for the observed increases in the rates at perimenopausal ages (40-55 yr). Although the magnitudes of mortality rates in Japan are about one fifth those in the West, they have been changing over time in much the same way as in the West. Cohort effects in incidence in Connecticut and Denmark also dipped around 1900. In Osaka, cohort effects rose from the cohort of 1901 to the cohort of 1936. (Author abstract) (43 Refs)

3. CANCER IN INDONESIA.

Sutnick AI, Gunawan S
Medical Coll. Pennsylvania, 3300 Henry Ave., Philadelphia, PA, 19129
JAMA; 247(22):3087-3088 1982

The health care system in Indonesia is outlined and analyzed briefly, and cancer incidence is discussed. Based on 'household survey techniques used from 1972-1980, the rising importance of cancer is suggested. Cancer of the uterine cervix and breast are the two most common types of cancer in Indonesia; cancer of the nasopharynx, liver, skin (especially of the legs and feet) and lung and choriocarcinoma are among the 10 most frequent. Various environmental factors that might influence cancer statistics are mentioned. The government of Indonesia is addressing the growing cancer problem through various programs. (2 Refs)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

4. SEX OF FIRST-BORN AS A RISK FACTOR FOR BREAST CANCER IN PRESENCE OF A POSITIVE FAMILY HISTORY (MEETING ABSTRACT)

Fournier P, Philippe P, Lalanne C
University of Montreal, Montreal, Quebec, Canada
Am J Hum Gen; 33(6):63A 1982

Recent studies appear to indicate that a first-born male child may be a prognosis factor for breast cancer. We have examined the role of this factor in the incidence of breast cancer both as an isolated risk factor and in combination with other known risk factors such as breast feeding, age at menarche, age at first birth, number of children, level of education, previous family history of breast cancer. Our study group comprised 77 breast cancer patients (mean age 57.6 years) and an age-adjusted control group of 75 non-cancer patients mean age (56.2 years). Our study showed that having a first-born male child did not in itself constitute a risk factor to breast cancer (Relative risk: 1.07). Conversely our study showed that when considered in relation to other known risk factors, a first-born male child did appear to confer a much higher risk towards breast cancer than if the other known risk factors operated in isolation. After adjustment by the Mantel-Haenszel method it was shown that past family history of breast cancer in mother or sister and a first-born male child conferred at 5 times higher risk of breast cancer. Past history of breast cancer in a first degree relative considered as an isolated confers a relative risk of 2. (no Refs)

5. FAMILY HISTORY AND ENDOMETRIAL CANCER (MEETING ABSTRACT)

Philippe P
University of Montreal, Quebec, Canada
Am J Hum Gen; 33(6):141A 1981

Preliminary results of a study designed to compare family history-positive (FH+) cases (with cancer of any site in 1st degree relatives) of endometrial cancer with their FH- counterparts (sporadic), are presented for the first 27 patients. The diagnosis of adenocarcinoma of the endometrium was confirmed in 26 probands (with one exception where a leiomyosarcoma was present); histopathological records of cancer in most 1st and 2nd degree relatives of probands were also searched. When compared to sporadic cases, FH+ probands proved to be less heavy and taller (thus less obese), were more fertile, had menarche later and were less frequently hypertensive. The FH+ group consistently showed more homogeneity on above features (except for family size) as pointed out by a lower variance. No difference, however, reached statistical significance. Despite low statistical power, the internal consistency of the results suggests that the classical epidemiological features of endometrial cancer more often pertain to its sporadic occurrence, thus reflecting a different physiopathological process. The relative rate of cancer in 1st and 2nd degree relatives of familial cases showed an excess of breast (19%), liver (11%), brain (8%), bone (8%) and pancreatic (8%) cancers, and a deficiency of lung cancers (8%). It is likely that the high prevalence of liver cancer is inflated (none confirmed yet) because of its highly metastatic nature. (1 Ref)

6. ENDOMETRIOSIS AND CANCER: CERTAIN COMMON FEATURES OF PATHOGENESIS AND BASIC PRINCIPLES OF TREATMENT.

Baskakov VP, Tsvelev IuV
S. M. Kirov Military Medical Acad., Leningrad, USSR
Vopr Onkol; 28(3):45-51 1982

Such features as single-phase cycling, endocrine infertility, endometriosis with concomitant endometrial hyperplasia, endometrial carcinoma and endometriosis with concomitant uterine myoma and proliferative processes in the mammary glands as well as hormono-metabolic disorders frequently occur both in endometriosis and endometrial carcinoma and, therefore, suggest that pathogenesis of these hormone-dependent diseases has something in common. It was established experimentally that the likelihood of proliferation development and malignancy in the endometrium is great, when it is dislocated and, particularly, when hormonal disorders occur. An autoimmune nature of endometriosis is suggested. The similarity and differences in diagnosis of endometriosis and some types of cancer as well as common principles of treatment of the diseases are discussed. It is recommended in conclusion that patients with endometriosis of the uterus, ovary and other sites should be referred to a group at high risk for cancer. (Author abstract) (30 Refs) (In RUS)

7. ASSESSING THE RISK FOR BREAST CANCER.

Jankowski NW, McBride CM, Moore A, Shirley RL, Smith F, Jankowski NW, Safford T
(c/o The Editor) Patient Care, 16 Thorndal Circle, Darien, CT, 06820
Patient Care; 16(5):21-23,30,32-34,43 1982

Current statistical status of breast cancer, general risk factors related to breast cancer, history of specific irradiation or drug therapy as a risk factor, and the role of benign disease in the development of breast cancer were discussed in a round table meeting. To date, no drug has been shown to increase the risk of breast cancer. Patients with fibroadenosis, sclerosing adenosis, blunt duct adenosis, apocrine metaplasia, plasma cell mastitis, and macrocystic disease have no associated risk of breast cancer. Mammographic reports of 'benign disease' were considered to be reassuring and normal. (6 Refs)

8. THE HIGH-RISK WOMAN.

Snyderman RK
Coll. Medicine/Dentistry, New Jersey-Rutgers Medical Sch., Univ. Heights, Piscataway, NJ, 08854
Breast Cancer 4 - Advances in Research and Treatment. McGuire WL, ed. New York, Plenum Medical Book Company, 234 pp., 1981.

The woman at high risk for breast cancer is described. Risk factors include a family history of breast cancer, frequent detection of masses requiring biopsy, a pathology report indicating premalignant lesion, and carcinoma of the other breast. Because detection methods available today are still unlikely to demonstrate breast cancer in time to prevent its development, prophylactic mastectomy should be considered for patients in the high-risk group. (10 Refs)

9. JUVENILE PAPILLOMATOSIS OF THE BREAST AND FAMILY HISTORY OF BREAST CARCINOMA.

Rosen PP, Lyngholm B, Kinne DW, Beattie EJ
Dept. Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer; 49(12):2591-2595 1982

Eighty-four patients included in the Juvenile Papillomatosis Registry were reviewed. The age of diagnosis ranged from 10-44 yr (mean, 21). Sixty-nine percent of patients were less than or equal to 20 yr of age. The left breast was affected slightly more often (52%) than the right (48%) when the lesion was unilateral. Two patients had bilateral lesions. Patterns of menarche, marital history, parity, and use of birth control pills were not exceptional for women in this age range. No instance was found of maternal use of estrogens during pregnancy. There were no instances of carcinoma developing after biopsy of juvenile papillomatosis, but a newly diagnosed patient had secretory carcinoma arising from juvenile papillomatosis. Two other examples of concurrent carcinoma were previously reported (ipsilateral lobular carcinoma in situ and contralateral secretory carcinoma). Particularly noteworthy is the finding that 26% of patients with information available reported that breast carcinoma had occurred in one or more female relatives. The majority were older, secondary relatives (grandmothers, great aunts), although maternal breast carcinoma (5 cases) was also reported. The mothers of both girls who had secretory carcinoma associated with juvenile papillomatosis had been treated for breast cancer. These findings, based on incomplete reporting, are cause for concern in two respects: the findings suggest that juvenile papillomatosis may be a marker for breast cancer for the patient's family, and they indicate a need for continued long-term follow-up of juvenile papillomatosis patients who may themselves be at increased risk. (Author abstract) (4 Refs)

10. SEX HORMONES AND GYNAECOLOGICAL CANCER.

Scott JS
Dept. Obstetrics and Gynaecology, Leeds Maternity Hosp., Leeds LS2 9NG, England
Br Med J; 284(6330):1657-1658 1982

The balance of risks and benefits of sexual intercourse is discussed in relation to cervical, breast, ovary, and endometrial cancers. Sexual activity may increase the rate of cervical cancer, but pregnancy and lactation aid in prevention of other gynecological cancers. Oral contraceptives and hormonal replacement may play a role in prevention of some cancers, but other, possibly negative effects have not yet been assessed. (16 Refs)

11. STUDIES ON THE COMPOSITION OF HUMAN BREAST CYST FLUID (MEETING ABSTRACT)

Yap PL, Miller WR, Roberts MM, Freedman B, Mirtle CL, Pryde AD, McClelland DB
University Department of Clinical Surgery, Royal Infirmary, Edinburhg EH3 9HB, Scotland
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

An increased risk of breast carcinoma exists in women with gross cystic disease of the breast (GCD), suggesting that the two diseases share a common etiology. We have therefore studied cyst fluid in an effort to discover its origin. Wide variations in the concentration of IgA, IgG, lactoferrin, lysozyme, albumin and dehydroepiandrosterone sulphate (DHAS) were found in 96 cyst fluids obtained from 75 patients with GCD. Sedimentation coefficient determinations performed on the 19 cyst fluids with the highest IgA concentrations indicated that 10 contained mainly 11S (secretory) IgA and resembled external mammary secretions such as colostrum and milk. These cysts also contained high concentrations of DHAS (80.9 mg/l;) but low concentrations of IgG and albumin. The remaining 9 cyst fluids resembled serum, with the IgA mainly of the 7S (serum) type, and these cysts contained low concentrations of DHAS (5.9 mg/l) but high concentrations of IgG and albumin. Other cyst fluids not analyzed by ultracentrifugation contained low concentrations of all the proteins measured. No relationship was observed between the concentrations of the substances studied, and clinical factors. The differing composition of cyst fluid suggests that components of the fluid may be derived from either serum or breast sources. There may therefore be more than one mode of cyst formation. (no Refs)

12. CHROMOSOMES, CANCER, AND RADIOSENSITIVITY (MEETING ABSTRACT)

Samouhos E
Radiation Therapy Service, Veterans Administration Medical Center, Martinez, CA, 94553
Am J Clin Oncol; 5(2):136 1982

Some specific chromosomal abnormalities are associated with certain cancers. The earliest description of such a specific association is that of the Philadelphia chromosome and myelogenous leukemia (1960). Other congenital karyotype abnormalities are associated with specific cancers. Examples are Down's syndrome with leukemia and Klinefelter's syndrome with male breast cancer. Genetic diseases of increased chromosome breakage, or of defective chromosome repair, are associated with greatly increased cancer incidence. Three such diseases have been recognized: 1) Fanconi's anemia, associated with leukemias and lymphomas; 2) Bloom's syndrome, associated with acute leukemias and lymphosarcoma; and 3) ataxia telangiectasia, associated with Hodgkin's disease, leukemia, and lymphosarcomas. Ten percent of individuals with ataxia telangiectasia will develop one of these neoplasms. Individuals with certain of these syndromes display an unusually high radiosensitivity. Radiation therapy for cancer has been fatal in patients who received as little as 3000 rad. This remarkable radiosensitivity has been quantitated in cell cultures from such cases. Evidence suggests that the apparent sensitivity may reflect subnormal ability to repair radiation damage. (no Refs)

13. BREAST IRRADIATION AND FUTURE RISK, EG CARCINOGENESIS (MEETING ABSTRACT)

Levitt SH

Department of Therapeutic Radiology, University of Minnesota Hospitals, Minneapolis, MN

Seventeenth Annual San Francisco Cancer Symposium, February 27-28, San Francisco, California West Coast Cancer Foundation; 1982

A major concern for physicians treating breast cancer patients with conservation surgery and radiation therapy is the possibility of the development of an increased incidence of second cancer in the contralateral breast and the treated breast. An analysis of the epidemiologic data related to the development of breast cancer was carried out, and the relative risks related to the dose of irradiation, the type of irradiation, the intent of the irradiation, and the age of the patient will be discussed. In addition, the clinical studies with the largest number of patients treated with radiation following breast cancer surgery with minimal and radical intent were reviewed. Based on these studies, the extent of risk of developing a second primary in the homolateral or contralateral breast is found to be minimal and not of such consequence that it would contraindicate the use of conservation surgery and radiation in the treatment of breast cancer. (no Refs)

14. HIGH RISK WOMEN: BREAST CANCER CONCERNS AND HEALTH PRACTICES (MEETING ABSTRACT)

Kelly PT

Mount Zion Hospital and Medical Center, San Francisco, CA

Seventeenth Annual San Francisco Cancer Symposium, February 27-28, San Francisco, California West Coast Cancer Foundation; 1982

Many women with a family history of breast cancer believe their risk of this disease is much higher than it actually is. They are unaware of the results of recent studies which show that not all women who have a mother or sister with breast cancer are a high risk. In fact, some women with an affected mother or sister have a risk that is no higher than that of the average woman. Among the factors that determine a woman's breast cancer risk due to family history are the ages (pre or postmenopausal) and laterality (unilateral or bilateral) of her affected relatives, and the pattern of disease occurrence in the family. As might be expected, women with a family history of breast cancer often have strong feelings about the disease. Some were profoundly affected by the sight of their relative's mastectomy scar. Others feel guilty about their treatment of affected relatives, fear for their own life and quality of life, or are angry about having to face a potentially fatal illness. Women's emotional reactions to breast cancer can prevent them from realistically confronting their risk, from practicing regular breast self-examinations and from establishing an effective health regimen for their breasts. Some ways to help these women are discussed. (no Refs)

15. GENETIC ANALYSIS OF FAMILIAL CANCERS (MEETING ABSTRACT)

White R, Barker D, Cavenee W, Skolnick M

Department of Cellular, Viral, and Molecular Biology, University of Utah School of Medicine, Salt Lake City, UT

Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

Families that have a marked predisposition to the development of specific tumors, such as retinoblastoma, Wilms' tumor, and colon and breast cancer, may carry and segregate specific alleles at loci that interact with the biochemical pathway and thus lead to tumorigenesis. Genetic analysis of these individuals at both the organismal and cellular levels will provide the basis for a molecular genetic approach to the etiology of such tumors. The necessity of knowing the genotype of both individuals and their tumors can be met by genetic markers based on DNA sequence polymorphism. Markers defining arbitrary loci can be used in familial studies to confirm the genetic basis of observed familial clustering and to examine genetic events in tumors. DNA segments containing suspected oncogenes (for example, the human equivalents of the genes defined in animal cells transformed by retroviruses or in cells transformed with DNA isolated from tumors) can be used to develop polymorphic restrction fragment markers and, in turn, to determine the role of such oncogenes in the primary etiology of familial tumors. We will report our progress in using these approaches to study retinoblastoma and colon cancers. (no Refs)

16. RISK FACTORS ASSOCIATED WITH BREAST CANCER. A RETROSPECTIVE EPIDEMIOLOGICAL STUDY.

Garcia-Sainz M, Borrego-Roman R, Diaz-Perches R
Hosp. de Oncologia, Centro Medico Nacional, Instituto Mexicano del Seguro Social, Mexico City, Mexico
Gac Med Mex; 117(8):323-331 1981

Risk factors for breast cancer were assessed in a group of 789 women without demonstrable breast pathology and 111 with adenocarcinoma of the breast. Age, marital status, and occupation were linked to cancer: 54% of the cancer patients were 60-79 yr old, and 35% were widowed. Single, younger women were more likely to be clerks, and married women and widows more likely to be housewives. Greater than 11 yr between menarche and first full-term pregnancy was a risk factor in this population. An even greater risk value was found for nulliparous women compared to those who had had 5 or more children. Breast feeding for the multiparous women was seen as a protective factor against breast cancer. Women who became menopausal after 55 yr of age are at greater risk than those who are menopausal by 45. A woman is at risk if her sister has had cancer but less so if the illness was contracted by a mother or aunt. However, in the Mexican population examined it was not possible to define a group of women who are at high risk for breast cancer. (19 Refs) (In SPA)

17. RISK FACTORS FOR EPITHELIAL OVARIAN CANCER IN ITALY.

Franceschi S, La Vecchia C, Helmrich SP, Mangioni C, Tognoni G
Inst. Pharmacological Res., Via Eritrea 62, 20157 Milan, Italy
Am J Epidemiol; 115(5):714-719 1982

In a case-control study conducted between May 1979 and February 1980, in Milan, Italy, to evaluate risk factors for ovarian cancer, various reproductive and menstrual characteristics, marital status, education, history of various diseases, and lifetime drug use were examined among 161 women with histologically proven epithelial cancer and 561 controls. Early menarche, late menopause, low parity, late age at first pregnancy and total ovulatory years were associated with an increased risk of ovarian cancer. The elevated risk associated with late age at first pregnancy was not accounted for by low parity. Many of the risk factors identified in this study are also related to the risk of adenocarcinoma of the endometrium and to breast cancer. Further exploration of these factors may lead to an improved understanding of the etiology of all three cancers. (Author abstract) (18 Refs)

18. HANDEDNESS AND BREAST CANCER LATERALITY: TESTING A HYPOTHESIS.

Howard J, Petrakis NL, Bross ID, Whittemore AS
NCI, Blair Building, Room 632, Bethesda, MD, 20205
Hum Biol; 54(2):365-371 1982

The tendency for breast cancer to occur more frequently on the left side may reflect the effect of handedness. If movement, related to handedness, is protective in terms of secretion and clearance of carcinogenic agents within the breasts, the relationship should be discordant. While the findings among 1,736 patients were consistent with the hypothesis, the effect was small and not statistically significant. The low proportion of left-handed women in the United States would indicate that a much larger sample is needed to adequately test the hypothesis. (15 Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

19. LEUKEMOID REACTION INDUCED BY DIFFERENT TRANSPLANTABLE TUMORS IN THREE INBRED MOUSE STRAINS.

Castillo R, Diaz JW, Veloso A, Gavilondo J
Natl. Inst. Oncology and Radiology, Havana 4, Cuba
Neoplasma; 29(1):73-79 1982

We have studied the induction of a granulocyte-associated leukocytosis (leukemoid reaction) in C3HA, C57Bl/6, and DBA/2 mice by a number of transplantable tumors of different origin. Leukemia L1210, Hepatoma 22, a transplantable mammary carcinoma of spontaneous C3HA origin, and a L929 culture fibroblasts-derived rhabdomyosarcoma, all induced a leukemoid reaction in their specific mouse strain. Melanoma B16 and Lewis lung carcinoma gave no reaction; Adenocarcinoma 755 and Harding-Pasey melanoma evoked a leukocytosis but not due to an increase in neutrophils. Some extratumoral factors can influence the hematological response; the intensity of final leukemoid reaction was higher in female mice than in males bearing the same tumor. On the other hand, Ehrlich ascites tumor transplanted in all three inbred mouse strains rendered different levels of leukemoid reaction; response was higher in DBA/2, intermediate in C3HA and lower in C57Bl/6. (Author abstract) (13 Refs)

20. TIME TO INDUCTION BY DIETHYLSTILBESTROL (DES) OF PALPABLE MAMMARY TUMORS IN C3H MICE (MEETING ABSTRACT)

Greenman DL, Farmer JH, Highman B
University of Arkansas Medical Science, Little Rock, AR
Toxicologist; 2(1):104 1982

To clearly define the dose response relationship for the DES induction of mammary tumors and to relate this to non-neoplastic responses to DES, over 2800 C3H/HeN(MTV+) female mice were fed DES for their lifetime at 0, 2.5, 5, 10, 20, 40, 80, 160, 320, and 640 ppb. Mice were palpated weekly for tumors and removed from study when masses reached a 1 cm diameter. Sacrifices were also schedules at 3 and 26 weeks. The crude incidences of histologically verifed mammary tumors for the dose-order listed above were 78, 84, 83, 83, 80, 80, 84, 86, 90, and 92%. These estimates were refined by simultaneously estimating non-parametrically the distributions of time-to-removal for 1 cm tumors (considered lethal) and for histologically verified tumors. Time adjusted estimates of mammary tumor incidence for each dose at 273 days were 75, 68, 67, 66, 67, 74, 81, 89, 99, and 100%, in dose order. The Peto test for dose related trends was significant for both distributions. Mice sacrificed at 3 and 26 weeks showed an apparent dose response for certain non-neoplastic endpoints. At both sacrifices, the prevalence of moderate to severe uterine glandular hyperplasia was not dose dependent and was less than 10% at 40 ppb DES or less, but the prevalence rose from 10-12% at 80 ppb to 100% at 320 or 640 ppb. (no Refs)

21. EXPERIMENTAL STUDY OF CARCINOGENICITY OF BASIC BLUE K.

Seliuzhitskii GV, Malysheva VV, Zus' BA
Medical Inst. Public Health, Leningrad, USSR
Gig Sanit; (4):30-32 1982

Carcinogenicity of the basic blue K dye was studied in albino rats. The animals were subjected to po administration (1-2x/wk, for 17 mo, total dose 1,044-1,236 mg) or to sc injections (single dose 7.8-11.7 mg, 1x/wk, for 66 wk). The av latent period of tumor development was 17 mo after po administration and 12 mo after sc administration. The incidence of tumor-bearing rats was 39.1% and 53.1%, respectively. The rats subjected to sc administration developed liposarcomas, while the rats undergoing po administration developed lymphosarcomas, hypernephroma, stomach leiomyoma, and mammary gland carcinomas. (2 Refs) (In RUS)

22. COMPARATIVE CARCINOGENICITY OF O-TOLUIDINE HYDROCHLORIDE AND O-NITROSOTOLUENE IN F-344 RATS.

Hecht SS, El-Bayoumy K, Rivenson A, Fiala E
Naylor Dana Inst. for Disease Prevention, American Health Foundation, Valhalla, NY, 10595
Cancer Lett; 16(1):103-108 1982

The carcinogenicity of o-toluidine hydrochloride (TOL) and o-nitrosotoluene (NTOL) in F-344 rats was evaluated. Mean weights were somewhat lower in the TOL and NTOL groups than in the control group. The mean daily doses of TOL and of NTOL (administered in the diet) were 0.062 g and 0.051 g, respectively. Food consumption was slightly less in the treated animals than in the animals fed the control diet. NTOL was significantly more effective than TOL in inducing hepatomas and bladder papillomas but was less active in the induction of mammary fibroadenomas. Both compounds induced significant numbers of fibromas of the skin and spleen as well as peritoneal tumors. The sc tumors were fibromas or mammary fibroadenomas. The peritoneal tumors were mesotheliomas and low grade spindle cell sarcomas. All invaded deeply into various abdominal organs and the muscular wall of the cavity. Most liver tumors were highly malignant hepatocarcinomas. Two rats displayed enormous multiple metastases of hepatoma tissue to the lungs. Bladder and pelvis-of-kidney tumors were of the usual transitional epithelium type. These results suggest that N-oxidation is important in the induction of bladder and liver tumors, while other metabolic conversions may play a role in the induction of other tumor types observed. (15 Refs)

23. ENHANCEMENT OF DMBA INDUCED MAMMARY TUMOURS BY INTERMITTENT WHOLE BODY HYPERTHERMIA (42 C).

Lahiri T, Deomina N, Dedov II, Lahiri P
Chittaranjan Natl. Cancer Res. Centre, Calcutta, India
Endocrinol Jpn; 28(5):569-574 1981

Effects of intermittent whole body hyperthermia (42 C) on dimethyl benz-anthracene (DMBA)-induced rat mammary tumors were determined in terms of tumor growth, plasma hormone levels, and activity of pituitary prolactin cells. Female Wistar (50-55 days old) rats were used. Heat exposure resulted in significant growth stimulation of the tumors in the majority (16/20) of heat-treated rats, compared to rats maintained at 25 C. The growth of tumors was generally intensified after 2-3 wk of heat stress and at the end of 6 wk an approx seven-fold increase in tumor vol was observed. Histological examination revealed that 18/20 animals in the control group and 17/20 in the treated group had adenocarcinoma type tumors. Other tumors were fibroadenomas and they were not included into the study. Body wt and wt of adrenal glands in heat-exposed rats were increased, while the wt of uterus and thymus was decreased. Plasma estradiol level in heat stressed animals was lowered while values for total thyroxine and thyroid stimulating hormone showed no fluctuation. Serum prolactin level was significantly increased in the heat exposed group. An electron microscopy study of prolactin cell activity of pituitary revealed that in heat stressed animals the activity was greater than in rats maintained at room temperature. Results indicated that whole body hyperthermia definitely enhances DMBA-induced mammary tumors in rats and the differences in response pattern might be related to the mode of heat application, etiology, or hormonal sensitivity of tumors. (20 Refs)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

24. INCREASE OF THE LIFESPAN AND DECREASE OF THE INCIDENCE OF TUMORS IN C3H/SN MICE TREATED WITH POLYPEPTIDE FACTORS FROM THE THYMUS GLAND AND PINEAL BODY.

Anisimov VN, Morozov VG, Khavinson VKh
N. N. Petrov Res. Inst. Oncology, Leningrad, USSR
Dokl Akad Nauk SSSR; 263(3):742-745 1982

To evaluate the possible relationship between aging and the state of immunity, female C3H/Sn mice were given injections of the polypeptide factors from the thymus (thymarin), pineal body (epithalamin) or from the anterior hypothalamus. The animals were followed up until the natural death. Prolonged administration of thymarin and epithalamin increased the lifespan of C3H/Sn mice by 2.5 and 3.5 mo, respectively. Administration of the polypeptide factors from the anterior hypothalamus decreased the lifespan by 2.5 mo. Thymarin and epithalamin slowed down the rate of aging. The incidence of mammary gland carcinomas in control C3H/Sn mice was 66.7%, compared with 24.0% after thymarin administration, 31.8% after epithalamin administration, and 38.9% after administration of the extract of the anterior hypothalamus. The mice treated with thymarin were free of leukemia, while 14.3% of the control mice developed leukemia. The specific antitumor effect of thymarin and epithalamin was associated with stimulation of cellular immunity: the indices of blast-transformation reaction in 9 mo old mice treated with thymarin and epithalamin were by 97% and 143%, respectively, greater than those in controls. (15 Refs) (In RUS)

25. CAFFEINE AND UNSATURATED FAT DIET SIGNIFICANTLY PROMOTES DMBA-INDUCED BREAST CANCER (MEETING ABSTRACT)

Minton JP, Foecking MK, Abou-Issa H
Ohio State University College of Medicine, Columbus, OH
Joint Meeting of the Society of Surgical Oncology and Society of Head and Neck Surgeons, April 18-23, 1982, Marco Island, Florida. The Society of Surgical Oncology and the Society of Head and Neck Surgeons 265 pp., 1982.

Caffeine is an important causative agent in the development of human fibrocystic breast and disease. The epithelial proliferation resulting from caffeine consumption has been shown to be reversible when caffeine abstention is carried out. The exposure of a well-established animal model to the known carcinogen dimethylbenz(a)anthracene (DMBA) is associated with the development of a hormone sensitive estrogen receptor positive breast tumor in nearly 90% of the animals. To determine the possibility of caffeine being an extraordinary promoter of breast cancer development in animals consuming vegetable fat the following study was carried out. A controlled study comparing the time to tumor development and the number of tumors and the growth rate of breast cancer in Sprague-Dawley rats which had been given 50 mg of DMBA at 6 weeks of age compared the tumor promotional effects of caffeine alone, caffeine and unsaturated fatty acids in combination, unsaturated fatty acids alone, and a standard rat chow diet. Twenty rats were in each group. The results show that the rat which consumed caffeine and unsaturated fatty acids had the earliest development of tumor, the most multiple tumor occurrence, and the most rapid rate of growth. Average time to development was 94 days. The fat and water rats had an average time of development of 133 and 140 days respectively. The caffeine alone rats had a mean time to tumor development of 188 days. The combination of an unsaturated fat diet and caffeine significantly shortened the time to tumor development when compared with the other three groups. (no Refs)

26. INFLUENCE OF DELAYED ADMINISTRATION OF RETINYL ACETATE ON MAMMARY CARCINOGENESIS.

McCormick DL, Moon RC
Lab. Pathophysiology, Life Sciences Div., IIT Res. Inst., Chicago, IL, 60616
Cancer Res; 42(7):2639-2643 1982

Administration of a dietary retinoid supplement beginning 1 wk after carcinogen administration is highly effective in the inhibition of rat mammary carcinogenesis. A study was designed at two carcinogen dose levels to determine to what extent retinoid feeding can be delayed and retain its chemoprotective effect. In the high-dose experiments, groups of 30 virgin female

Sprague-Dawley rats received a single iv dose of 50 mg N-methyl-N-nitrosourea (MNU) per kg body wt and were fed a dietary supplement of 328 mg retinyl acetate per kg diet beginning at 1, 4, or 8 wk after MNU administration. In the low-dose experiment, groups of 50 rats received 25 mg MNU per kg, and the retinoid was begun at 1, 4, 8, 12, 16, or 20 wk post-MNU. Controls at both dose levels received a placebo diet beginning 1 wk after carcinogen treatment. At the high MNU dose, retinyl acetate was most effective in inhibition of carcinogenesis when treatment was begun 1 wk after MNU administration. Delaying retinyl acetate feeding until 4 wk post-MNU resulted in slightly reduced chemoprotective efficacy, while an 8-wk delay caused a complete loss of anticancer activity. At the low MNU dose, delaying retinyl acetate administration for up to 12 wk after MNU administration caused no loss of chemopreventive efficacy. A 16-wk delay resulted in decreased anticancer activity, while retinoid treatment begun 20 wk post-MNU had no effect on cancer induction. Retinoid administration can be delayed beyond 1 wk and retain its activity against rat mammary carcinogenesis; the length of delay allowable without loss of activity is a function of tumor latency. (Author abstract) (15 Refs)

27. EFFECTS OF DIETARY LIPIDS ON LACTOGENIC HORMONE RECEPTOR BINDING IN RAT MAMMARY TUMORS.

Cave WT, Erickson-Lucas MJ
Endocrine Unit, Dept. Internal Medicine, Univ. Rochester Sch. Medicine, St. Mary's Hosp., 89 Genesee St., Rochester, NY, 14611
JNCI; 68(2):319-324 1982

Both epidemiologic studies in humans and experiments in laboratory animals have indicated that high-fat (HF) diets promote mammary tumor growth; however, the biochemical mechanisms responsible for this accelerated tumor growth are poorly understood; thus this study was designed to determine whether diet-induced alterations in the lipid composition of mammary tumor cell membranes were associated with differences in lactogenic hormone binding capacity. Mammary tumors were induced with N-methyl-N-nitrosourea in 50-day-old female inbred Buffalo rats that were maintained on either HF or low-fat (LF) diets composed of either 20% corn oil or 0.5% corn oil, respectively. The microsome-membrane fractions of these tumors were then analyzed for specific lactogenic hormone binding with the use of 125I-labeled human growth hormone. Methylated extracts of these same membrane fractions were also subjected to gas-liquid chromatography. Our results demonstrated that the mammary tumor membranes of the HF group did have a significantly greater lactogenic binding capacity than those of the LF group and that these differences in hormone binding were accompanied by significant alterations in the membrane qualitative fatty acid profiles of each group. Therefore, one way in which dietary lipids may be able to influence mammary tumor growth is by modification of the lactogenic hormone binding capacity of tumor cell membranes. (Author abstract) (27 Refs)

28. POTENTIATION OF THE THYMOSIN IMMUNOREGULATORY EFFECT BY HYPOCORTICOIDISM IN RATS WITH DMBA-INDUCED CARCINOGENESIS IN MAMMARY GLANDS.

Grinevich YA, Kamenets LY
Kiev Roentgen-Radiological and Oncological Res. Inst., Health Ministry of Ukrainian SSR, 252022 Kiev, USSR
Neoplasma; 29(1):19-27 1982

Effect of adrenalectomy and/or thymosin administration on the tumor growth and immunity system were investigated on the models of 7,12-dimethylbenz(a)anthracene(DMBA)-induced mammary neoplasms in rats. Adrenalectomy and thymosin administration resulted in antitumorigenic action, whereas maximal inhibiting effect was achieved after thymosin injection in adrenalectomized animals. The maximal antitumorigenic effect of thymosin in adrenalectomized rats was accompanied by synergistic immunopotentiating effect of thymosin and adrenalectomy. Immunorehabilitation with thymosin and simultaneous correction of hormone production in the adrenal cortex are believed to enhance the effectiveness of therapy in cancer patients (Author abstract) (29 Refs)

29. SELENIUM, ESTRADIOL 17BETA, NITRITES, AND HUMAN BREAST CANCER.

Lombard LF
11145 Northborough Lane, Richmond, VA, 23235
Med Hypotheses; 8(4):371-382 1982

An hypothesis postulating an etiology of breast cancer from interactions among selenium, estradiol 17beta, nitrites, and RBC is presented. In this hypothesis, in the presence of nitrites, triglycerides, and selenium, estradiol 17beta is catalyzed by an unknown enzyme (' X') to form the known carcinogen chrysene, which is complexed with methemoglobin in the RBC. The conversion process may partially take place in the gastrointestinal tract and liver, with more direct conversion in breast cells after transport. Chrysene, in the breast cells, already under attack by nitrites or lysosomal enzymes, causes additional focal hyperplasia, metaplasia, neoplasia, anaplasia, gene alteration, and carcinoma. The process may also require high androgen levels and other trace elements, such as zinc. (51 Refs)

30. MARROW TUMOR INTERACTIONS: THE ROLE OF THE BONE MARROW IN CONTROLLING CHEMICALLY INDUCED TUMORS. PROGRESS REPORT, JULY 1, 1980-JULY 31, 1981.

Klimpel GR, Scuderi P, Pollack SB, Ching LM, Mule JJ
Washington Univ., Seattle, WA
Marrow Tumor Interactions: The Role of the Bone Marrow in Controlling Chemically Induced Tumors. Progress Report, July 1, 1980-July 31, 1981. Available from National Technical Information Service, Springfield, VA, as DE81030317:, 23 pp., 1981.

Progress is outlined below. (1) Bone marrow has been shown to uniquely contribute to the neutralization of immunogenic, chemically induced neoplasms by producing Natural Tumor Growth Regulatory cells. These cells are not differentiated T or B lymphocytes, recognizable by conventional markers, nor are they apparently macrophages. Current work will characterize these cells (2) Experimental evidence shows that the bone marrow can generate cytotoxic T lymphocytes in vitro on a much larger scale than previous systems have been able to document. The development and refinement of in vitro assays will resolve what role each of these cell types contributes to the antitumor effect mediated by bone marrow cells. (3) CE mammary carcinoma has been shown not to generate immunity detectable by conventional assays. Studies will continue to test whether or not the mammary carcinoma engages immune responses, perhaps through the expression of viral antigens. (4) The development of immunogenic methylcholanthrene induced sarcomas in BALB/c x CE F1 mice which support the mammary carcinoma now enables testing whether or not growing neoplasms influence bone marrow functions. (5) Tests have demonstrated that the mammary carcinoma alters cell populations of lymphocytes in lymphoid organs and is mainly a consequence of reduced lymphocyte production by the bone marrow. (6) Studies continue on the effect tumors exert on hemopoiesis. (Author abstract)

31. INHIBITION OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED TUMORS IN SYRIAN HAMSTERS BY PRIOR INFECTION WITH H-1 PARVOVIRUS.

Toolan HW, Rhode SL, Gierthy JF
Inst. Medical Res. Bennington, Bennington, VT, 05201
Cancer Res; 42(7):2552-2555 1982

Hamsters, given injections, sc at birth of H-1 parvovirus and 1 mo later given a single injection of 7,12-dimethylbenz(a)anthracene, had a 38% tumor incidence compared with a 95% incidence in animals receiving 7,12-dimethylbenz(a)anthracene alone. Thus, H-1 which, it has already been shown, invokes a resistance to the incidence of spontaneous and adenovirus-induced neoplasms in hamsters also produces a suppression of a carcinogen-induced tumor in these animals; this suggests that the H-1-induced barrier to successful oncogenesis by these diverse agents has a common mechanism which, present experiments indicate, is not related to a positive or negative H-1 serology. The pathology of the 7,12-dimethylbenz(a)anthracene-induced tumors was similar for both control and H-1-infected hamsters. Although all but one of the primary neoplasms were anaplastic fibrosarcomas as reported previously by others, 25% of the affected females had, in addition, mammary adenocarcinomas, an extremely rare tumor in hamsters. (Author abstract) (26 Refs)

32. CALORIE RESTRICTION: EFFECT ON GROWTH OF HUMAN TUMORS HETEROTRANSPLANTED IN NUDE MICE.

Giovanella BC, Shepard RC, Stehlin JS, Venditti JM, Abbott BJ
Stehlin Foundation for Cancer Res., 777 St. Joseph Professional Building, Houston, TX, 77002
JNCI; 68(2):249-257 1982

The presence of four human malignant tumors (1 breast, 1 lung, and 2 colon carcinomas) growing sc as heterotransplants in nude mice did not significantly affect the body wt of adult animals until the tumors reached very large dimensions (tumor wt greater than 15% of the body wt). However, a colon carcinoma (HT 29) induced a cessation of the natural rate of body wt increase when it grew in young adults (animals weighing approx 25 g which will gain 6 g or approx 25% body wt in 1 mo). Calorie restriction at all the levels tested (8, 6, 4, and 2 g/day/mouse) with standard pelletized mouse food produced both wt loss in the animals (with and without tumor) and a lowering of the growth rate of all the four tumors tested growing at a sc site and/or under the kidney capsule. Each tumor responded differently to calorie restriction. The four tumors tested grew equally in both male and female nude mice. Young animals weighing 20 g inoculated with a fifth tumor (MeWo melanoma) exhibited tumor growth inhibition proportional to restriction of calorie intake. Their survival, however, did not improve. (Author abstract) (41 Refs)

33. ON THE RELATIONSHIP BETWEEN NUTRITION AND THE DEVELOPMENT OF TUMORS.

Kolb E
Wissenschaftsbereich Tierbiochemie, Karl-Marx-Universitat Leipzig, Semmelweisstrasse 4, DDR-7010 Leipzig, E. Germany
Z Gesamte Inn Med; 37(6):169-176 1982

Chronic intake of carcinogens and cocarcinogens in the diet is a primary factor in the development of tumors in humans. High intake of meats has been linked to cancers of the colon and breast. Reduction in intake of animal fats to less than 50 g/day and increase in intake of raw fibers and carotenes are recommended. Small amounts of smoked meat and fish are not considered to be harmful. Foods containing aflatoxins from fungi should be avoided. (50 Refs) (In GER)

34. EFFECT OF SELENIUM ON THE INDUCTION OF BREAST FIBROADENOMAS BY ADENOVIRUS TYPE 9 AND 1,2-DIMETHYLHYDRAZINE-INDUCED BOWEL CARCINOGENESIS IN RATS.

Ankerst J, Sjogren HO
Wallenberg Lab., Univ. Lund, Lund, Sweden
Int J Cancer; 29(6):707-710 1982

Selenium in its organic and inorganic forms has been shown to inhibit the development of chemically induced, spontaneous and transplanted tumors. The present investigation was performed to study the effect of selenium (4 ug per ml of drinking water) on tumorigenesis of adenovirus-type-9-induced breast fibroadenomas and on 1,2-dimethylhydrazine-induced bowel carcinogenesis in WF rats. It was found that identical treatment with Se under identical conditions and with no obvious toxic effects on the rats (1) resulted in inhibition of DMH-induced large-bowel carcinogenesis; (2) facilitated induction of small-bowel cancer by the same carcinogen in the same animals, and (3) greatly facilitated induction of breast fibroadenoma by adenovirus Type 9 in the same strain of rats. The effect of Se treatment on DMH-induced large-bowel carcinogenesis confirms previous findings and proves that the opposite effect on fibroadenoma development is not due to differences in eg effective dose, animal strains or condition of the animals. It is not yet clear through which mechanisms Se exerts these effects. (Author abstract) (29 Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

35. HORMONES AS ETIOLOGICAL AGENTS IN NEOPLASIA.

Furth J
Inst. Cancer Res., Columbia Univ. Coll. Physicians and Surgeons, New York, NY
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Hormones as etiological agents in neoplasia are discussed. The basic properties of human hormones are reviewed, and general considerations in the detection of hormonal activity are listed. Brief general comments are presented on tumors in peripheral areas illustrating the diversity of pathogenic mechanisms by which hormones can produce tumors. Peripheral tumors are of two kinds: those affecting non-hormone-secreting organs, which do not feed back (as with the mammary gland), and those affecting peripheral hormone-secreting organs, which do. The best example of the former is the mammary tumor, and good examples of the second type are thyroid and ovarian tumors. Other tumors which are hormonally related include adrenal tumors which are unique in that they can give rise to four or more types of tumors - estrogen, androgen, glucocorticoid, and mineralocorticoid secreting - and in that they have different types of inductive mechanisms. Renal cortical carcinomas are induced by estrogens in male hamsters. Human placental lactogen stimulates carcinogenesis in young rats. It promotes mammary tumorigenesis during pregnancy, both directly and indirectly, through its promotion of progesterone secretion by the ovary. Thyrocalcitonin is the hypocalcemic polypeptide hormone secreted by the medullary cells of the thyroid. These cells can give rise to medullary thyroid carcinoma. (286 Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

36. IDENTIFICATION OF AN ANTIGEN ASSOCIATED WITH TRANSFORMING GENES OF HUMAN AND MOUSE MAMMARY CARCINOMAS.

Becker D, Lane MA, Cooper GM
(c/o Cooper), Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Proc Natl Acad Sci USA; 79(10,part1):3315-3319 1982

Sera from tumor-bearing mice immunoprecipitated an 86,000-dalton glycoprotein from extracts of NIH cells transformed by human mammary carcinoma DNA. This antigen was not immunoprecipitated from extracts of NIH 3T3 cells, spontaneously transformed NIH cells, NIH cells transformed by normal human DNA, NIH cells transformed by human bladder carcinoma DNA, or NIH cells transformed by Rous sarcoma virus DNA. In addition, sera from mice bearing tumors induced by NIH cells transformed by either normal human DNA or human bladder carcinoma DNA did not immunoprecipitate this antigen from extracts of NIH cells transformed by human mammary carcinoma DNA. However, this antigen was immunoprecipitated by sera from mice bearing tumors induced by NIH cells transformed by mouse mammary carcinoma DNAs and from mice bearing primary mammary carcinomas. These results indicate that this glycoprotein represents an antigen that is specifically associated with expression of the transmissible transforming genes of human and mouse mammary carcinomas. (Author abstract) (15 Refs)

37. SIMULTANEOUS DETERMINATION OF T-ANTIGEN AND ABO CELL SURFACE ANTIGENS IN TRANSITIONAL CELL CARCINOMA (MEETING ABSTRACT)

Kidd D, Javadpour N, Fourcroy J, O'Connel K
No affiliation given
77th Annual Meeting of the American Urological Association, Inc., May 16-20, 1982, Kansas City, Missouri. American Urological Association 254 pp., 1982.

The purpose of this study was to investigate the changes in cell surface antigens which result in the interruption of communication and interaction through the cell surface membrane. These changes reflect an alteration in the genome which modifies the biosynthetic pathways of the Golgi apparatus. The demonstration of T-antigen expression in breast carcinoma and the loss of blood group iso-antigens in invasive transitional cell carcinoma prompted inquiry into the correlation between the carbohydrate precursor of the human blood system MN and the epithelial surface blood group isoantigens. A red cell adherence assay to detect T-antigen on deparafinized slides of transitional cell carcinoma of the bladder was developed. Peanut agglutinin which has anti-T properties as well as other nonspecific binding sites is layered over the slides, washed, then covered with neuraminidase treated red cells. Red cell adherence was noted on areas of the bladder tumor that binds plant lectin. This was compared with the specific red cell adherence (SRCA) for ABO antigen on the same tissue samples. Of the 17 patients, 14 demonstrated loss of their cell surface ABO antigens. Of the 14, 28% demonstrated expression of the T-antigen. This would imply that T-antigens may be complementary to A, B, O, Ag in predicting potential malignancies of bladder cancer when the conventional histologic examination can not provide any prediction. (no Refs)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

38. CONSERVATION OF PROTEIN CODING POTENTIAL IN THE LONG TERMINAL REPEATS OF EXOGENOUS AND ENDOGENOUS MOUSE MAMMARY TUMOR VIRUSES.

Peters G, Smith R, Brookes S, Dickson C
Imperial Cancer Res. Fund Lab., Lincoln's Inn Fields, London WC2A 3PX, England
J Virol; 42(3):880-888 1982

In vitro protein synthesis and DNA sequence analysis indicate that mouse mammary tumor virus differs from other well-characterized retroviruses in that the long terminal repeat region of the provirus has the capacity to encode proteins. Different exogenously transmitted mouse mammary tumor virus strains and endogenous proviral units conserved this open reading frame feature in the long terminal repeat despite a variation in nucleotide sequence. The proteins encoded by the different long terminal repeats were clearly related, but showed minor variations in size and tryptic peptide maps. In each case, the largest in vitro product had a mol wt of about 36,000 to 37,000, suggesting that the open reading frame sequences must extend for approx 1,000 nucleotides beginning at the extreme 5' end of the long terminal repeat. The fact that the reading frame was conserved among these viruses argues in favor of an in vivo function for the open reading frame protein. (Author abstract) (29 Refs)

39. GENE REGULATION AND ONCOGENESIS BY RETROVIRUSES (MEETING ABSTRACT)

Varmus HE
Department of Microbiology and Immunology, University of California, San Francisco, CA
Thirty-fifth Annual Symposium on Fundamental Cancer Research, March 2-5, 1982, Houston, Texas. The University of Texas M. D. Anderson Hospital and Tumor Institute 38 pp., 1982.

We studied the functional capacities of long terminal repeats (LTRs) by constructing recombinant plasmids, which contain LTRs and cloned genes in various arrangements, and then introducing them into cultured cells. As expected, only an LTR in the correct transcriptional orientation upstream from a promoter-less gene can produce expresson of that gene. However, when the gene carries its own promoter, the efficiency of DNA transformation is enhanced manyfold by the presence, in either orientation, of certain LTRs suggesting that some LTRs may enhance gene expression at distant, heterologous promoters in a nonpolar fashion. The LTR of mouse mammary tumor virus (MMTV) governs expression of viral or linked cellular genes in a glucocorticoid-responsive manner; the region responsible for hormonal regulation has been localized to about

0.4 kb near the 3' end of the MMTV LTR. The induction of B-cell lymphomas by avian leukosis virus (ALV) appears to require insertion of proviral DNA near c-myc, a putative cellular oncogene. The viral inserts, sometimes comprising little more than a single LTR, can enhance expression of c-myc in at least three arrangments: When positioned upstream from c-myc in the same transcriptional orientation, the inserts are promoters for the transcription of c-myc; when positioned upstream in the opposite orientation to c-myc or downstream in the same orientation, they enhance expression from unidentified cellular promoter(s). In the last instance, the LTR provides a novel site for polyadenylation. Interrupted c-myc loci have been cloned from tumor DNA and reintroduced into cultured cells to identify determinants of the enhancement phenomena. (no Refs)

40. MURINE MAMMARY TUMOR VIRUS-RELATED ANTIGEN IN HUMAN MALE MAMMARY CARCINOMA (MEETING ABSTRACT)

Lloyd RV, Rosen PP, Sarkar NH, Jimenez D, Kinne DW
Department of Pathology, University of Michigan, Ann Arbor, MI
71st Annual Meeting of the International Academy of Pathology (United States-Canadian Division), March 1-5, 1982, Boston, Massachusetts. International Academy of Pathology 95 pp., 1982.

An antigen immunologically related to mouse mammary tumor virus (MuMTV) and the major envelope glycoprotein, gp52 of MuMTV, was identified in tissue sections of human male and female mammary carcinomas using the peroxidase-antiperoxidase technique. Positive reactions with the gp52 antiserum were seen in mouse and human mammary carcinomas but not in normal mammary tissues, mammary tissues with benign diseases, and in other primary malignant neoplasms. Almost all of the 32 of 36 (89 per cent) male mammary carcinomas were positive for the gp52-related antigen, whereas 14 of 50 (28 per cent) of tumors from female patients were positive. The gp52-positive tumors were significantly larger than the gp52-negative tumors in female patients. Gp52-positive tumors were also larger than gp52-negative tumors in male patients, but the difference was not statistically significant. Gp52 reactivity was also detected in metastatic mammary carcinoma in axillary lymph nodes of male and female patients. The presence of gp52-related antigen was not apparently related to tumor grade or lymphocytic infiltrate in the primary tumor. (no Refs)

41. ML ANTIGEN OF DBA/2 MOUSE LEUKEMIAS: EXPRESSION OF AN ENDOGENOUS MURINE MAMMARY TUMOR VIRUS.

Racevskis J, Sarkar NH
Lab. Molecular Virology, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
J Virol; 42(3):804-813 1982

Spontaneous, transplantable leukemias of DBA/2 mice express an antigen (ML) which cross-reacts with antigens of murine mammary tumor virus (MuMTV). The MuMTV cross-reactive antigen of the DBA/2 leukemias (ML cells) was found to be a glycoprotein of 78,000 mol wt containing antigenic determinants of the major MuMTV glycoprotein gp52. No MuMTV particles were produced by the ML cells, although they did contain type A particles - the pronucleocapsids of MuMTV. The ML antigen appeared to be an aberrant form of the intracellular MuMTV env precursor molecule prgp70, which was not processed properly but instead acquired extra carbohydrate groups and was expressed in uncleaved form on the cell surface. Isolation of MuMTV core protein p28 from the leukemic cells and subsequent tryptic peptide mapping analysis showed that the p28 from leukemia cells differed from the p28 of MuMTV isolated from DBA/2 mouse milk. These observations indicate that the MuMTV expressed in DBA/2 leukemic spleen cells is of a different strain than the virus secreted in lactating mammary glands of DBA/2 mice and probably represents the expression of an endogenous DBA/2 provirus. (Author abstract) (34 Refs)

42. MURINE MAMMARY TUMOR VIRUS-RELATED ANTIGEN IN HUMAN MALE MAMMARY CARCINOMA (MEETING ABSTRACT)

Lloyd RV, Rosen PP, Sarkar NH, Jimenez D, Kinne DW
Departments of Pathology, Molecular Virology and Surgery, University of Michigan, Ann Arbor, MI
Lab Invest; 46(1):50A 1982

An antigen immunologically related to mouse mammary tumor virus (MuMTV) and the major envelope glycoprotein, gp52 of MuMTV, was identified in tissue sections of human male and female mammary carcinomas using the peroxidase-antiperoxidase technique. Positive reactions with the gp52 antiserum were seen in mouse and human mammary carcinomas but not in normal mammary tissues, mammary tissues with benign diseases, and in other primary malignant neoplasms. Almost all of the 32 of 36 male mammary carcinomas were positive for the gp52-related antigen, whereas 14 of 50 of tumors from female patients were positive. The gp52-positive tumors were significantly larger than the gp52-negative tumors in female patients. Gp52-positive tumors were also larger than gp52-negative tumors in male patients, but the difference was not statistically significant. Gp52 reactivity was also detected in metastatic mammary carcinoma in axillary lymph nodes of male and female patients. The presence of gp52-related antigen was not apparently related to tumor grade or lymphocytic infiltrate in the primary tumor. (no Refs)

43. ULTRASTRUCTURE OF THE CYCLING UTERUS IN A HIGH MAMMARY TUMOR AND A LOW MAMMARY TUMOR STRAIN OF MOUSE (MEETING ABSTRACT)

Brophy MO, Spring-Mills E
Department of Anatomy, Upstate Medical Center, Syracuse, NY
Anat Rec; 202(3):22A 1982

The mammary gland in the low tumor strain of mouse, C3HeB/FeJ, displays a more consistent and regular pattern of branching at all stages of development than the mammary gland of the high tumor strain of mouse, C3H/HeJ. The high tumor mouse infects its young with the mouse mammary tumor virus (MMTV) via its milk; the low tumor strain does not. The MMTV can be identified in electron micrographs of the mammary epithelium of infected animals. In order to test whether the differences in mammary gland structure between the high tumor and the low tumor strain of mouse were due to a direct effect of the viral particles in the epithelial cells or to a generalized effect of the virus on the hormonal milieu, we compared the uterine morphology in these two strains of mice. Vaginal smears were made and the mammary glands, ovaries, oviducts and uterus from 26 C3H/HeJ and 34 C3HeB/FeJ mice, aged 8 to 20 weeks, were prepared for light and electron microscopy. Preliminary evidence indicates that the eosinophilic band which is apparent in the apical cytoplasm of the uterine epithelial cell in late diestrus and proestrus with the light microscope is composed of many small empty vesicles located just beneath the lumenal surface. By the end of metestrus II, the vacuoles are decreasing in number and size, and contain less material. Although the estrus cycle pattern is similar in both the high and low tumor strain of mouse, the uterine ranges are more consistent and regular in the low tumor strain of mouse. (no Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

44. EVIDENCE OF A PHOSPHORYLATED PROTEIN SPECIFIC OF HUMAN COLON CARCINOMA CELLS.

Munsch N, Raux H, Fondaneche MC, Burtin P
Inst. de Recherches Scientifiques sur le Cancer, B.P. 8, 94802 Villejuif Cedex, France
Biochem Biophys Res Commun; 106(1):87-93 1982

Two human tumor cell lines, HT29 and Caco2, and the mammary tumor cell line MDA -MB-231 synthesize in culture a 42 kilodalton (42K) protein detectable by immunoprecipitation. This protein, which is phosphorylated in the two colon tumor cell lines, is not detectable by antisera against normal adult colon, suggesting that the 42K protein represents a tumor specific antigen. Addition of a differentiating agent, retinoic acid, reduces the growth of the tumor cells by 50%, but has no effect on the expression of the 42K protein. (10 Refs)

45. HIGH FREQUENCY OF IN VIVO SISTER CHROMATID EXCHANGES IN THE BONE MARROW CELLS OF MICE BEARING MAMMARY ADENOCARCINOMA DBRB.

Banerjee R, Goldfeder A, Mitra J
(c/o Goldfeder) Cancer and Radiobiological Res. Lab., New York Univ., New York, NY, 10003
Cancer Genet Cytogenet; 5(4):321-326 1982

Sister chromatid exchanges (SCEs) in vivo were evaluated in the bone marrow cells of mice bearing mammary adenocarcinoma dbrB of 0.5 and 1.0 cm3, respectively. It has been observed that the SCE frequency is significantly higher (p less than 0.001) in the bone marrow cells of tumor-bearing mice as compared to the bone marrow cells of non-tumor-bearing mice. SCE frequency in the bone marrow cells of mice with 1.0-cm3 tumors did not increase appreciably with tumor size as compared to that in the bone marrow cells of mice with 0.5-cm3 tumors. This indicates the presence of mammary carcinoma-induced somatic stress as noted in the genetic material of the bone marrow cells of the host. (Author abstract) (31 Refs)

46. COVALENT CROSS-LINKING OF A PHOTOACTIVE DERIVATIVE OF CALCITONIN TO HUMAN BREAST CANCER CELL RECEPTORS.

Moseley JM, Findlay DM, Martin TJ, Gorman JJ
Dept. Medicine, Univ. Melbourne, Repatriation General Hosp., Heidelberg, Victoria, 3077, Australia
J Biol Chem; 257(10):5846-5851 1982

A photoaffinity derivative of salmon calcitonin has been produced by transglutaminase-mediated incorporation of N-(beta-aminoethyl)-4-azido-2-nitroaniline into the hormone. The derivative, purified by high pressure liquid chromatography, retained the abilities to bind to cultured T47D breast cancer cells and to stimulate adenylate cyclase in these cells. In both these respects it was equipotent with synthetic salmon calcitonin. Photolysis of the 125I-labeled photoactive salmon calcitonin derivative bound to T47D cells was accompanied by specific labeling to only one component (Mr = 85,000) as assessed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Labeling was observed only upon photolysis and was inhibited by unlabeled synthetic salmon calcitonin but not by the inactive calcitonin analogue, 8-glycine human calcitonin. Reduction did not alter the apparent mol wt of the calcitonin receptor complex. No macromolecular forms of calcitonin were produced by photolysis in the absence of T47D cells. (Author abstract) (29 Refs)

47. IMMUNOPEROXIDASE LOCALIZATION OF LACTALBUMIN IN MALIGNANT BREAST NEOPLASMS.

Clayton F, Ordonez NG, Hanssen GM, Hanssen H
(c/o Ordonez) Dept. Pathology, Texas Medical Center, Univ. Texas, M. D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Arch Pathol Lab Med; 106(6):268-270 1982

By an immunoperoxidase method, lactalbumin was demonstrated in the cytoplasm of epithelial cells of normal breast, primary and metastatic breast carcinomas, and benign breast disease. Lactalbumin was present in 39 of 64 breast carcinomas of different types, including 77% (31) of infiltrating ductal carcinomas and 42% (7) of infiltrating lobular carcinomas. It also was present in 55% (nine) of metastatic breast carcinomas and in 100% (5) of fibroadenomas. Lactalbumin was not observed in normal tissues and malignant neoplasms of other tissues, indicating that lactalbumin can serve as a specific tissue marker for malignant neoplasms of the breast and their metastases. (Author abstract) (16 Refs)

48. DIFFERENCES IN BINDING AMONG LECTINS TO LESIONS OF THE BREAST (MEETING ABSTRACT)

Franklin WA
Department of Pathology, University of Chicago, Chicago, IL
Lab Invest; 46(1):26A 1982

The distribution of lectin-binding carbohydrate was assessed by fluorescence microscopy in 20 breast lesions including seven scirrhous ductal carcinomas, one infiltrating lobular carcinoma, one colloid carcinoma, four fibroadenomas, and six cases of fibrocystic disease. Tissue sections were stained with biotinylated wheat germ agglutinin (WGA), Ricin communis agglutinin I (RCA I), peanut agglutinin (PNA), Dolichos biflorus agglutinin (DBA), Ulex europeus agglutinin I (UEA I) and concanavalin A (Con A), and with fluorescein-conjugated avidin. In benign lesions, lectin-binding carbohydrate was localized mainly along the apices of mammary epithelial cells. The distribution of lectin-binding carbohydrate in malignant tumors was variable and carbohydrate could be found in the cytoplasm and along the margins of tumor cells. Considerable variation was found among the lectins in their binding to breast tumors with strongest and most consistent staining obtained with WGA, followed in order of staining intensity by RCA I, PNA, SBA/DBA, and Con A. UEA I stained many of the benign breast lesions but no malignant lesions. (no Refs)

49. CARCINOEMBRYONIC ANTIGEN AND ALPHA-LACTALBUMIN IN BREAST CARCINOMA: AN IMMUNOHISTOCHEMICAL STUDY (MEETING ABSTRACT)

Kuhajda FP, Mendelsohn G
Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD
Lab Invest; 46(1):46A 1982

Carcinoembryonic antigen (CEA) is a valuable marker in many carcinomas, whereas alpha-lactalbumin (ALA), a protein produced by breast epithelial cells, is specific for breast carcinoma. Conflicting reports exist concerning CEA and ALA in different histologic types of breast carcinoma. To evaluate the distribution and staining characteristics of these markers, we stained 62 assorted in situ and infiltrating breast carcinomas, numerous benign breast lesions, and normal breast tissue using the immunoperoxidase technique. Positive immunostaining for CEA was observed in 62 per cent of carcinomas, but not in normal breast or benign breast lesions including papillomas and duct papillomatosis. ALA was present in 76 per cent of carcinomas and focally positive in normal breast epithelium and in four papillomas. In situ lobular carcinoma stained poorly for both CEA and ALA; ALA was present in 77 per cent of infiltrating lobular carcinomas, whereas CEA was present in only 32 per cent. There was no significant difference in CEA and ALA staining in lymph node metastases from 14 patients. However, lymph node metastases were more frequent in cases of infiltrating duct carcinoma with strong CEA positivity. (no Refs)

50. CORRELATION OF ESTROGEN RECEPTOR LEVELS WITH DNA-DEPENDENT RNA POLYMERASE ACTIVITY IN 7,12-DIMETHYL BENZ(A)ANTHRACENE (DMBA)-INDUCED MAMMARY TUMORS IN RATS (MEETING ABSTRACT)

Hunter JB, Mohla S
Department of Oncology and Pharmacology, Howard University Cancer Center, Washington, DC, 20060
Med Pediatr Oncol; 10(1):101 1982

Approximately 60% of breast cancer patients have estrogen receptors (ER) of which two thirds respond favorably to hormonal therapy. Estrogens act on their target tissues by interacting with their cytoplasmic receptors, followed by translocation of the estrogen receptor complex into the nucleus. This results in increased RNA synthesis as evidenced by increased RNA polymerase activity. Using DMBA-induced mammary tumors in rats, experiments were designed to see whether RNA polymerase activity of isolated tumor nuclei may be related to their cytoplasmic ER levels. Mammary tumors were induced by a single intragastric feeding of 15 mg DMBA in 1.5 ml peanut oil. Mammary tumors were analyzed for ER using dextran coated charcoal or sucrose density gradient methods. Tumor nuclei were isolated using fresh, minced tissue and analyzed for RNA polymerase activity as previously described. Seventyseven percent (10/13) of ER positive greater than 10 femto moles/mg protein) tumors exhibited low RNA polymerase activity (less than 200 pico moles of 3H-UMP/mg DNA). In contrast 83% (5/6) of ER negative (less than 10 femto moles/mg protein) tumors showed high RNA polymerase activity (greater than 200 pico moles of 3H-UMP/mg DNA). Similarly, the incorporation of 3H-AMP into RNA was lower (less than 200 pico moles/mg DNA) in 91% (10/11) of ER positive tumors, whereas the majority of ER negative tumors (63%) showed higher (greater than 200 pico moles/mg DNA) 3H-AMP incorporation. The incorporation of 3H-GMP into RNA also exhibited a similar correlation to ER. These data suggest additional biochemical parameters to distinguish between ER positive and ER negative tumors. (1 Ref)

51. METABOLISM OF BENZO(A)PYRENE BY HUMAN EPITHELIAL AND FIBROBLASTIC CELLS: METABOLITE PATTERNS AND DNA ADDUCT FORMATION.

Bartley J, Bartholomew JC, Stampfer MR
Peralta Cancer Res. Inst., Peralta Hosp., Oakland, CA
J Cell Biochem; 18(2):135-148 1982

The metabolism of benzo(a)pyrene (BaP) and DNA adduct formation were compared in the same incubations of mammary epithelial cells grown out in early passage, from each of three human subjects, and of fibroblasts from one of these subjects. Mammary epithelial cells showed the preferential formation of 7,8-dihydrodiol-9,10-dihydroepoxybenzo(a)pyrene, (BPDE) the ultimate carcinogen. The end products of BaP metabolism in fibroblasts, unlike epithelial cells, were mainly mono- and dihydroxide derivatives of BaP. The greater ease of DNA adduct formation in epithelial cells is apparently related to the metabolites produced from BaP by these cells. The metabolite results indicate that mammary epithelial cells preferably converted BaP to diols, some of which were conjugated with glutathione at the first epoxidation step. The remaining dihydrodiols were readily converted to BPDE, a large portion of which ended up as tetrols and glutathione conjugates, but in the process BPDE was available to react with DNA. The accumulation of diols in the later stages of fibroblast incubations indicates that these cells have a much lower capacity to convert diols to the diolepoxide than do mammary epithelial cells. These results support the theory that chemical carcinogens may be involved in the induction of human breast cancer. (46 Refs)

52. RELATIONSHIPS BETWEEN STEROID RECEPTOR AND EPITHELIAL CELL PROLIFERATION IN BENIGN FIBROCYSTIC DISEASE OF THE BREAST.

Jacquemier JD, Rolland PH, Vague D, Lieutaud R, Spitalier JM, Martin PM
Dept. Pathology, Institut Paoli-Calmettes, 232 Bld Sainte-Marguerite, F 12273 Marseille Cedex 2, France
Cancer; 49(12):2534-2536 1982

Tissue specimens from 27 patients with mammary fibrocystic disease were assayed for estrogen (ER) and progestin (PR) receptors. Seventeen patients (63%) had ER-positive lesions (greater than 5 fmol/mg protein). A progression in ER presence was noted from fibrocystic disease (33%) and fibrosing adenosis (50%) to lobular and ductal hyperplasia (85%). Similarly, ER content increased from 14.5 +-13 fmol/mg cytosol protein in fibrocystic disease and fibrosing adenosis to 31.5 +-23 fmol/mg protein in epithelial hyperplastic lesions. Furthermore, the ER-PR couple was only encountered in lobular and ductal hyperplasia. The authors' data indicate that the incidence of steroid receptor parallels the intensity of hyperplasia in benign breast disease. (Author abstract) (15 Refs)

53. PITUITARY RESPONSES TO THYROTROPIN-RELEASING HORMONE AFTER TREATMENT WITH THE BREAST CARCINOGEN NITROSOMETHYLUREA: INHIBITION OF PROLACTIN BUT NOT THYROTROPIN RELEASE.

Kieffer JD, Maloof F, Vickery AL, Mover H, Downing M, Ridgway EC
Thyroid Unit, Massachusetts General Hosp., Boston, MA, 02114
Endocrinology; 110(6):1892-1896 1982

N-Nitrosomethylurea (NMU) is a widely used experimental breast carcinogen. The present report describes the effects of NMU on the plasma PRL and TSH increases in response to exogenous TRH. Female Buffalo rats, 75-80 days old, were given a single ip injection of NMU (10 mg/100 g) or vehicle. At various times after injection, NMU-treated rats and vehicle-injected controls were tested with exogenous TRH (625 ng/100 g, ip). Groups of four to six rats were bled at 10, 20, 30, 45, and 60 min after TRH and at 10 min after saline (baseline group). The response to TRH (delta) was determined by subtracting the mean plasma PRL or TSH level of the baseline group from the mean peak level observed after TRH. For four separate control experiments, deltaPRL averaged 104 +-19 ng/ml (mean +- SE). At 20 hr, 42 hr, 6 days, and 2, 3, 4, 8, and 12 wk after NMU, deltaPRL was 87, 0, 0, 16, 10, 3, 49, and 65 ng/ml, respectively. deltaPRL was statistically significant in all four control experiments, and remained significant at 20 hr after NMU. However, from 42 hr through 4 wk, no significant deltaPRL occurred. A significant deltaPRL reappeared at 8 and 12 wk, the approximate time of appearance of the first palpable breast cancers. Pituitary PRL concentrations (micrograms PRL per mg protein) were significantly lower in NMU-treated groups than in vehicle-treated controls at 42 hr, 3 wk, and 12 wk. In contrast to its marked inhibitory effect on deltaPRL, NMU had no effect on deltaTSH. This is consistent with the hypothesis that treatment with NMU resulted in a selective impairment of pituitary PRL-secreting cells. Moreover, our data show that the plasma PRL response to TRH was inhibited at times after NMU when pituitary PRL was not significantly depleted. This observation is in accord with the concept of impairment of either TRH receptor binding or events which couple receptor binding and hormone release. (Author abstract) (38 Refs)

54. RECEPTOR BINDING AND PROCESSING OF EPIDERMAL GROWTH FACTOR BY HUMAN BREAST CANCER CELLS.

Osborne CK, Hamilton B, Nover M
Dept. Medicine, Univ. Texas Health Science Center, San Antonio, TX, 78284
J Clin Endocrinol Metab; 55(1):86-93 1982

Epidermal growth factor (EGF) stimulates the growth of human breast cancer cells (MCF-7). To better define the mechanisms for these effects, we studied receptor binding and subsequent processing of [125I]EGF in cells growing in monolayer culture under conditions in which an effect on growth is observed. Binding was temperature dependent and was higher at reduced temperature. At 37 C, binding rapidly reached a maximum (20-60 min) and then gradually decreased. Binding was slower at a reduced temperature. High affinity was demonstrated by the ability of unlabeled EGF to compete for [125I]EGF binding; half maximal displacement was observed at an EGF concentration that also resulted in half-maximal biological activity (1-2 ng/ml). Scatchard plots derived from these data or from those of studies using increasing concentrations of [125I]EGF were curvilinear and superimposable. Plots from binding data obtained at 0 C were also curvilinear, suggesting that the processing and degradation of tracer alone cannot explain this finding. Other peptides did not compete for EGF binding. During a 6-hr incubation, progressive degradation of [125I]EGF occurred on and/or in the cells, with prompt release of low mol wt fragments into the medium. Furthermore, during this time, the bound intact EGF became more resistant to dissociation by excess unlabeled EGF. Reduced binding (50%), not due to simple occupancy, was also noted during a 2-hr preincubation with unlabeled EGF, indicating down-regulation of receptor. These data suggest the following sequence of events. At 37 C, EGF rapidly binds to specific receptors on MCF-7 cells. The bound EGF becomes more and more difficult to dissociate from the cell, and the number of available receptors is reduced, implying sequestration in the cell membrane and/or internalization of the hormone-receptor complex. Gradually, EGF is degraded, and the products are released from the cell. Human breast cancer appears to be a target for EGF action. (Author abstract) (24 Refs)

55. GROWTH FACTORS FOR CULTURED MAMMARY AND FIBROBLASTIC CELLS (MEETING ABSTRACT)

Rudland PS, Smith JA
Ludwig Institute, Royal Marsden Hospital, Sutton, Surrey, England
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

The growth of the mammary gland is controlled by a series of interacting mammotrophic hormones. However these hormones are relatively inactive compared with serum or novel, semi-purified growth factors (GF) in stimulating cell proliferation of cultured rat mammary gland epithelial cells. These GF's are of two types, a pituitary GF exerting systemic control and GF's from surrounding cells which may exert local control of mammary epithelial cell proliferation. The effects of the GF's can be amplified by certain mammotrophic hormones (eg insulin: I and hydrocortisone: HC). As in the mammary gland, GF's such as FGF, EGF, PGF2 alpha (fibroblast growth factor, epidermal growth factor, prostaglandin F2alpha) can stimulate DNA synthesis in quiescent 3T3 fibroblasts and this can be modified with I and HC. To explain the kinetics obtained with PGF2 alpha and FGF two operational signals are postulated, signal (1) initiates a lag phase and signal (2) determines the magnitude of the rate of cellular entry into the S phase of the cell cycle. Usually the rate of entry into S governs the rate of cell division, but when serum is completely removed additional components (eg transferrin) are required. During the lag phase the pathways generated by signal (1) and signal (2) have to interact causing increases in hypothetical protein(s) inside the cell. One of the altered properties of virally transformed cells is their lack of response to GF's. In the two cases examined by other groups the viral transforming proteins directly act on the putative intracellular pathways leading to increased cell proliferation rates. (no Refs)

56. CYCLIC AMP BINDING PROTEINS, OESTROGEN RECEPTORS AND PROGESTERONE RECEPTORS IN HUMAN BREAST CANCER (MEETING ABSTRACT)

Watson D, Hawkins RA, Senbanjo R, Telford J, Forrest AP
Department of Clinical Surgery, University of Edinburgh, Edinburgh, Scotland, Miller, W. R.
Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

While human breast cancer which possess estrogen receptor (ER) and progesterone receptor (PgR) activities are likely to be hormone responsive, many do not respond to endocrine therapy. In hormone-dependent rat mammary tumors the ratio of cyclic AMP binding proteins to steroid receptors may better discriminate hormone dependent from independent tumors than steroid receptors alone. The inter-relationships between cyclic AMP binding protein, ER and PgR activities have therefore been determined in 100 human cancers. Cyclic AMP binding was detected in all tumors, ER in 70 and PgR in 38. Mean cyclic AMP binding level in ER negative tumors was significantly higher than in the ER positive group. In tumors with both activities there was no significant correlation between levels of binding. Similar relationships were also found between cyclic AMP binding and PgR. Expressing results as ratios of ER to cyclic AMP binding proteins neither divided the tumors into obvious subgroups nor discriminated between PgR positive and negative tumors. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

57. BIOPHYSICAL ASPECTS OF RADIATION CARCINOGENESIS.

Kellerer AM, Rossi H
Institut fur Medizinische Strahlenkunde, Univ. Wurzburg, Wurzburg, W. Germany
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Radiation is termed 'ionizing' when its interactions are so energetic that they remove electrons from the atoms that constitute the irradiated matter. In the case of many materials - including tissues - this leads to permanent changes that are produced with far greater efficiency than is obtained with radiations that merely induce electronic or molecular excitations. Ionization occurs through the agency of electrically charged particles that may be high-speed electrons or nuclear constituents such as protons and alpha-particles. The principal process determining the range of charged particles is electronic collision. The rate of energy loss of charged particles is known as the linear energy transfer which is only an av, characterizing a complicated process. The track of an ionizing particle consists of primary ionizations produced in close proximity to the geometrical trajectory and secondary ionizations that surround this path up to highly variable distances. The physical quantity which is of central importance in radiobiology is the absorbed dose, and the rad is the unit of absorbed dose. Many radiobiological phenomena and at least one type of radiation carcinogenesis are due to tissue response to radiation injury. Findings on the induction of mammary neoplasms demonstrate a complexity of the process of radiation carcinogenesis that is also reflected in the variety of often complicated dose-effect relations observed in other experimental animal studies. (103 Refs)

58. RADIATION CARCINOGENESIS.

Storer JB
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN
Cancer - A Comprehensive Treatise Vol. 1. Etiology - Chemical and Physical Carcinogenesis. Second Edition. Becker FF, ed. New York, Plenum Press, 714 pp., 1982.

Ionizing radiation in sufficiently high dosage acts as a complete carcinogen in that it serves as both initiator and promoter. Cancers can be induced in nearly any tissue or organ of man or experimental animals by the proper choice of radiation dose and exposure schedule. Myeloid leukemia and the acute leukemias are probably the most easily induced of all radiation-induced neoplasms. Unlike solid tumors of other tissues with a long latent period, the leukemias occur early, show a high incidence, and then fall close to the control incidence. The other relatively easily induced tumor in human populations is cancer of the thyroid, particularly when the radiation is delivered to juveniles. Breast cancer can also be induced by radiation exposure but higher doses are required for its induction. Evidence that the lung is moderately sensitive to cancer induction is provided principally from studies of uranium miners occupationally exposed to radon. The salivary gland is moderately sensitive to cancer induction, and a few have been reported as being radiation-induced. Cancer of the skin was a frequent sequela to exposure to very large doses of radiation received by earlier x-ray workers who were unaware of the hazards of radiation exposure. Like skin, bone is resistant to cancer induction, even though a large number of radiation-induced sarcomas have been reported. Physical factors that effect carcinogenesis include dose rate, radiation quality, internal emitters vs external exposure, total body and partial body exposure, and host factors. (103 Refs)

59. CURRENT VIEWS ON HORMONES AND BREAST CANCER.

Molinatti GM, Limone P
Cattedra di Endocrinologia, Universita di Torino, C.so Polonia, 14, 10126 Turin, Italy
Minerva Med; 73(17):1047-1053 1982

Recent studies on relationships between hormone status and breast cancer in women are reviewed. The pathophysiological aspects of estrogens, prolactin, dehydroepiandrosterone and dehydroepiandrosterone sulfate and therapeutic significance of estrogen and prolactin receptors are discussed. (57 Refs) (In ITA)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. TOXICITY OF POLYBROMINATED BIPHENYLS (PBBS) IN DOMESTIC AND LABORATORY ANIMALS.
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IARC Sci Publ (40): 347 pp., 1981.

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EPIDEMIOLOGY OF HUMAN BREAST CANCER

1. BREAST CANCER IN NEW YORK STATE. TRENDS IN FEMALE MORTALITY, 1970-1977.

Notani PN, Varma AO, Leske MC, Janerich DT
Dept. Community and Preventive Medicine, State Univ. New York at Stony Brook, Stony Brook, NY, 11794

NY State J Med; 82(7):1044-1049 1982

Breast cancer mortality in the New York State counties (exclusive of New York City) was analyzed for the period 1970 through 1977 for white and nonwhite females. While the mortality rate for white females (32 per 100,000) did not change over this period, the mortality for nonwhites increased from 17 per 100,000 in 1970 to 24 per 100,000 in 1977. On examination of age-specific trends, the increased mortality for nonwhites

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over time was evident at all age groups over 30 yr, whereas for whites an increase was observed only for women over 80 yr. Up to age 40, age-specific mortality for whites and nonwhites was about the same, with nonwhites showing slightly higher rates than whites. After 40 yr, however, there was a sharp and consistent rise in mortality with age for whites but not for nonwhites (mostly blacks). A similar pattern was observed in the national breast cancer incidence and mortality of white and black females. The difference in postmenopausal breast cancer rates for whites and blacks may be due to differences in reproductive patterns and life-style, with factors such as diet possibly playing a role. Differences in breast cancer mortality were observed among the counties, with rates being highest in Nassau, Suffolk, and Erie counties. Multiple regression analysis of breast cancer mortality for white females by county revealed a strong association with high population density areas. This variable explained 69% of the variation in rates, with regression coefficient being positive and significant. (Author abstract) (18 Refs)

2. AN EPIDEMIOLOGIC STUDY OF BREAST CANCER IN POSTMENOPAUSAL WOMEN ACCORDING TO THE LEVEL OF ESTROGEN RECEPTOR IN THE TUMOR.

Hildreth NG
Yale University, New Haven, CT
Diss Abstr Int [B]; 42(12,pt1):4754-B 1982

This case-control study has examined the epidemiology of breast cancer with regard to the level of estrogen receptor in the tumor. Breast cancer cases and controls were postmenopausal women aged 45-74 years who were admitted to two hospitals in New Haven, Connecticut. A standardized structured questionnaire administered by trained interviewers was used to collect data on demographic variables, reproductive and menstrual histories, use of exogenous estrogens, family history of female cancers, body build indicators, and a history of certain illnesses and surgical procedures. All breast tumors were assayed similarly in one laboratory for estrogen receptor. An analysis of the cases alone identified five factors associated with the level of estrogen receptor in the tumor, the latter being considered both as a dichotomous (estrogen receptor positive versus estrogen receptor negative) and as a continuous (logarithm of the estrogen receptor concentration) variable. Tumors were more likely to be estrogen receptor positive and were more likely to have a higher mean estrogen receptor concentration among women with any of the following characteristics: nulliparity, having had a late age at first live birth, having had a history of benign breast disease, and having breastfed at least one child. Use of estrogen replacement therapy was associated with a greater likelihood of the tumor being estrogen receptor negative and having a lower mean estrogen receptor concentration. A case-control analysis distinguishing cases according to the estrogen receptor status of the tumor and focussing specifically on these five factors suggests that the epidemiology of estrogen receptor positive and estrogen receptor negative breast cancers may be dissimilar in some respects. With regard to the etiology of breast cancer, further support is provided for a central role of estrogens. (no Refs)

3. BREAST CANCER EPIDEMIOLOGY AT PRESENT.

Morales S A
Epidemiolgo del Servicio de Salud Norte y del Ministerio de Salud, Chile
Bol Hosp San Juan Dios; 29(1):16-23 1982

Data from the early 1900's to the present on various epidemiological factors relating to breast cancer are studied. Menarche at an early age is considered a protective factor and prolonged use of estrogens a risk factor. Women who are multiparous and experience their first term pregnancy before the age of 24 yr are less likely to develop breast cancer. The role of breast-feeding as a protective factor was found to be secondary to the significance of the age at first pregnancy. There is a protective factor in early menopause. A small proportion of breast cancers found within families has been related to an autosomal dominant gene on Chromosome 10. Diets high in saturated fats and body surface measurements are risk factors. Socioeconomic factors, use of hair dyes, and exposure to ionizing radiation were also considered. The highest occurrence rate was found in the United States, Canada, and Northeastern Europe. In Chile, the mortality rate of breast cancer as compared to all other cancer mortalities is 5%. The highest occurrence rate is in the cities. (15 Refs) (In SPA)

4. CANCER AMONG BLACKS IN NEWARK, NEW JERSEY, 1970-1976. A NATIONAL AND INTERNATIONAL COMPARISON.

Thind IS, Najem R, Paradiso J, Fuerman M
Dept. Preventive Medicine and Community Health, New Jersey Medical Sch., Coll. Medicine and Dentistry, 100 Bergen St., Newark, NJ, 07103
Cancer; 50(1):180-186 1982

Newark black men had age-adjusted cancer rates comparable to those of Washington, DC, but lower than the other three American city blacks. Rates for Newark black women were generally similar to other American black women. American blacks, like those of Newark, had cancer rates higher than the African blacks in three out of four countries studied. Only blacks of Rhodesia had cancer experience like that of American blacks. Except for cancer of the cervix, the African blacks had generally lower rates compared to the American blacks for the 10 sites investigated. However, high rates did occur for certain sites, eg, esophagus and bladder cancers in Bulawayo, Rhodesia. Newark blacks also had higher rates for certain sites (prostate, lung, breast and cervix) compared to Washington, DC, and certain other US cities. Thus, the total risk of malignancies to develop among Newark blacks was no greater than that expected, based upon the four US cities' experience. (Author abstract) (39 Refs)

5. TRENDS IN CANCER INCIDENCE: CAUSES AND PRACTICAL IMPLICATIONS. PROCEEDINGS OF A SYMPOSIUM HELD OSLO, NORWAY, 6-7 AUGUST 1980.

Magnus K
The Cancer Registry Norway, Montebello, Oslo 3, Norway
Trends in Cancer Incidence: Causes and Practical Implications, Proceedings of a Symposium held Oslo, Norway, 6-7 August 1980. Washington, D. C., Hemisphere Publishing Corporation, 446 pp., 1982.

Time trends in cancer incidence are described and analyzed. Methodological aspects reviewed include a description and reliability of trends in cancer incidence (Arcadian normal; problems in cancer incidence trends in the United States; time trends, cohort effects, and aging as influencing factors; concurrent trends in etiological research) and implications of trends in cancer incidence (interrelationships of incidence, survival, and mortality and their effects on time trends; time trends as indicators of etiology; prediction of cancer incidence based on cohort analysis; prediction of cancer incidence by utilization of risk factors and the effect of intervention). Incidence trends of stomach cancer in the five Nordic c[illegible]ies, in Osaka, in the United States, and the recession of [illegible]mach cancer are discussed. Cancer of the larynx and lung are discussed with respect to incidence trends and alcohol consumption and tobacco usage, recent changes in pattern of occurrence of oat cell carcinoma of the lung, and trends of mortality from lung cancer in women. Breast cancer incidence trends in Nordic countries, in North America, Japan, and Hawaii, and in Europe and Israel, and during a course of periodic screening are reviewed. Trends of uterine cervical cancer are reviewed for the Nordic countries, Sweden, Iceland, and Canada. Trends in prostatic cancer in Nordic countries and in the Americas are discussed. Malignant melanoma of the skin is discussed with respect to time trends, and incidence trends in the Nordic countries, Finland, Australia, and Israel. (470 Refs)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

6. GENETIC/EPIDEMIOLOGICAL FINDINGS IN A STUDY OF SMOKING-ASSOCIATED TUMORS.

Lynch HT, Fain PR, Albano WA, Ruma T, Black L, Lynch J, Shonka M
Dept. Preventive Medicine and Health, Creighton Univ. Sch. Medicine, 2500 California Street, Omaha, NB, 68178
Cancer Genet Cytogenet; 6(2):163-169 1982

While the etiology of bronchogenic carcinoma remains enigmatic, an expanding array of carcinogenic pollutants in interaction with host susceptibility factors has been implicated. We have studied family histories of cancer in a consecutive series of cancer patients from two university oncology clinics in Nebraska. Particular attention has been given to carcinoma of the lung and other putative smoking-associated cancers (oral cavity, esophagus, urinary bladder, pancreas). Smoking histories were obtained for relatives of an overlapping series of patients with these tumor sites. Findings revealed that, although a significant cohort effect was observed with respect to smoking habits for both relatives of lung cancer probands and for relatives of probands with other smoking-associated tumors, a corresponding trend for lung cancer frequency was observed only for relatives of lung cancer probands. This result suggests the importance of host factors in combination with environmental exposures in determining lung risk. A cohort trend for lung cancer was also apparent among relatives of breast cancer probands, but not for relatives of colon cancer probands, suggesting the possibility of an intrinsic association between carcinomas of the breast and lung. We believe that further elucidation of host factor susceptibility in lung cancer may have important etiological and preventive implications. (Author abstract) (38 Refs)

7. OBESITY, ANDROGENS, ESTROGENS, AND CANCER RISK.

Kirschner MA, Schneider G, Ertel NH, Worton E
Newark Beth Israel Medical Center, 201 Lyons Ave., Newark, NJ, 07112
Cancer Res; 42(8,Suppl):3281s-3285s 1982

Obesity is associated with increased incidence of cancers arising from tissues responsive to estrogenic stimulation, including endometrium, breast, and prostate. We thus wished to explore estrogen production and its origin in obesity in an attempt to provide a possible hormonal link to explain increased cancer risk. Studies of the hormonal milieu of obese men and women revealed several abnormalities of sex hormone production and metabolism. (a) Androstenedione production rates are elevated and serve as prehormones of both testosterone and estrogens. (b) Extragonadal aromatization of androgens to form estrogens (androstenedione to estrone and testosterone to estradiol) is elevated, resulting in (c) increased production rates of estrogens. The obese person is thus chronically exposed to hyper-estrogenemia. In addition, obesity is associated with other alterations of sex hormone metabolism such as decreased levels of sex hormone-binding globulin and increased metabolic clearance rates of several hormones. After weight loss to ideal body weight, there appears to be normalization of androgen and estrogen production rates, as well as circulating hormone levels; however, metabolic abnormalities such as increased aromatization of androgens to estrogens and accelerated metabolic clearance rates of androstenedione remain abnormal. (Author abstract) (65 Refs)

8. EPIDEMIOLOGY OF BREAST CARCINOMA III: RELATIONSHIP OF FAMILY HISTORY TO TUMOR TYPE.

Rosen PP, Lesser ML, Siene RT, Kinne DW
Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer; 50(1):171-179 1982

Previous breast carcinoma in at least one female relative was reported by 31% of 1,024 women treated consecutively for breast carcinoma at Memorial Hospital. Eighty (7.9%) of their mothers had had breast cancer. Maternal breast cancer was significantly (p less than 0.006) more frequent among women with medullary carcinoma than those with other tumor types and among those who were pre- or perimenopausal at diagnosis (p less than 0.001). Among the 727 patients who had one or more sisters, 12% had a sister who had been treated for breast cancer. The highest frequency of carcinoma in at least one sister occurred in patients with lobular carcinoma while the medullary carcinoma group had the least number of patients with an affected sister (p less than 0.03). Occurrence of breast cancer in a sister was almost twice as common in patients who were postmenopausal at diagnosis (p less than 0.005) than in premenopausal patients. When stratified by histologic type, the mean age at diagnosis of the patients did not differ appreciably from the age at diagnosis of their sisters. Detailed analyses of histologic type and other more distant familial relationships were also obtained but were considered to be less reliable because of problems in ascertainment and there were fewer affected relatives. No single histologic type of carcinoma was consistently linked to a disproportionately high or low frequency of carcinoma in all classes of relatives. It is possible that studies of family history limited to information available when the patient is first treated present an incomplete picture of familial aggregation. Further follow-up after diagnosis is needed to obtain a more reliable measure of the extent to which relatives are affected by breast cancer and patterns of family distribution associated with specific tumor types. (Author abstract) (16 Refs)

9. RELATIONSHIP OF OBESITY TO BLOOD ESTROGENS.

Zumoff B
Div. Endocrinology and Metabolism, Dept. Medicine, Beth Israel Medical Center, New York, NY, 10003
Cancer Res; 42(8,Suppl):3289s-3294s 1982

It has become conventional wisdom that estrogenic stimulation of breast tissue has something to do with the causation of breast cancer and that the reason obesity is a risk factor for breast cancer is that obese women are hyperestrogenized. However, it has been very difficult to demonstrate that excessive exogenous estrogen increases the incidence of breast cancer, that endogenous estrogen excess is present in breast cancer, or that obese women are hyperestrogenized. We have examined the last question by measuring 24-hr mean plasma estrone and estradiol levels in the midfollicular phase in 18 healthy, regularly cycling, very obese (53 to 218% above ideal weight) women and 16 regularly cycling, age matched, nonobese control women. Unlike obese men, the obese women showed no significant elevation of either estrone or estradiol. Their av estrone level was 72 compared with 64 pg/ml in controls; their average estradiol level was 65 compared with 57 pg/ml in controls. In the combined group (obese plus nonobese), there was a significant correlation of percentage of deviation from ideal weight with plasma estrone ($y = 63 + 0.12x$; p less than 0.05) but not with estradiol. This correlation supports the current hypothesis that there is increased androstenedione/estrone conversion (ie, increased aromatase activity) in obesity. The reason plasma estrone levels are not significantly elevated in obese women is that the small amount derived from androstenedione is swamped by the much larger amount derived from ovarian secretion, which is apparently unaffected by obesity. Unless there is increased local formation of estrogens in the breast tissue of obese women, the absence of elevated plasma estrogens in them means that their breasts are not 'seeing' increased estrogen levels. Thus, endogenous hyperestrogenization is unlikely to be a causative factor of breast cancer in obese women. (Author abstract) (48 Refs)

10. GENETICS AND BREAST CANCER.

Lynch HT
Dept. Preventive Medicine, Creighton Univ. Sch. Medicine, Omaha, NE
Genetics and Breast Cancer. New York, Van Nostrand Reinhold Company, 253 pp., 1981.

The etiologic role of genetic factors in breast cancer (BC) are discussed with regard to epidemiology, biostatistics, genetics, pathology, and endocrinology. In addition, programs for counseling, surveillance, and management of hereditary BC patients and high-risk individuals are presented in context with site-specific BC pedigrees as well as those that reflect differing patterns of familial tumor associations such as breast/ovarian cancer syndromes. Practical technics are described to help identify patients genetically prone to BC. The risks of birth control pills, other pharmaceuticals, and radiation (as in xeromammography), are, where appropriate, compared with evidence at the infrahuman level. Hormonal studies contrasting high genetic risk with low genetic risk patients are described. Other topics covered include genetic determinants of BC susceptibility, a statistical model for the study of familial BC, pathologic aspects, patient and family management of familial BC, genetic heterogeneity hormones, and purposes, technics, and procedures relating to particular types of breast surgery. (578 Refs)

11. PRE- AND POSTMENOPAUSAL BREAST CANCER.

Najem GR, Rush BF, Miller FW, Dimarco PE, Roellke SE, Grobstein N, Levitt JW
Dept. Preventive Medicine, MSB-F516, Univ. Medicine and Dentistry of New Jersey, 100 Bergen St., Newark, NJ, 07103
Prev Med; 11(3):281-290 1982

Age at menarche, parity, age at first full-term birth, breast feeding patterns, age at menopause, and history of oral contraceptive use were investigated in a case-control study involving 60 breast cancer patients and 125 matched controls from the same New Jersey screening population. Significant associations were found between the presence of other cancers in relatives, oral contraceptive use, and weight of subjects, and incidence of breast cancer, but no significant associations were found between age at menarche, age at first full-term birth, age at menopause, parity, or menopausal status. (25 Refs)

12. TRAUMA AS A RISK FACTOR FOR BREAST CANCER.

Bazhenova AP, Ostrovskaia IM, Lipkovich VS
P. A. Hertsen Res. Oncological Inst., Moscow, USSR
Khirurgiia (Mosk); (5):6-8 1982

Of 150 patients with breast cancer, 11 had a history of breast trauma. The time period between trauma and development of tumor or appearance of the bloody discharge from the nipple ranged from 2.5 mo to 2 yr. Majority of the patients (71%) with post-traumatic breast cancer were in Stages I and IIa. Histologically, one patient had intraductal carcinoma, three had adenocarcinomas, three had solid carcinomas, two had scirrhous carcinomas, one had malignant mesenchymoma, and one had malignant fibroadenoma. (9 Refs) (In RUS)

13. CYCLIC OVARIAN FUNCTION AND BREAST CANCER.

Sherman BM, Wallace RB, Bean JA
Dept. Internal Medicine, Univ. Iowa, Iowa City, IA, 52242
Cancer Res; 42(8,Suppl):3286s-3288s 1982

We postulated previously that systematic differences in menstrual cycle length and/or variability might be used as indicators of underlying hormonal abnormalities that could help explain the endocrine biology of some breast cancer risk factors. In the present study, we prospectively and retrospectively analyzed menstrual cycle patterns in breast cancer cases and controls in two populations. No significant differences were found. This and previous studies emphasize that contemporary women have a long reproductive experience characterized by uninterrupted, regular menses, which is a condition of maximum ovulation potential and which contributes to estrogen stimulation over time. (Author abstract) (25 Refs)

14. DIET IN THE EPIDEMIOLOGY OF BREAST CANCER.

Graham S, Marshall J, Mettlin C, Rzepka T, Nemoto T, Byers T
Dept. Social and Preventive Medicine, State Univ. New York at Buffalo, 2211 Main St., Buffalo, NY, 14214
Am J Epidemiol; 116(1):68-75 1982

A variety of studies have shown that diets high in fat, particularly polyunsaturated, have enhanced the production of tumors in animals challenged with chemical carcinogens. Other studies have found an apparent contradiction of no difference in the incidence of breast cancer among women with varying levels of serum cholesterol as measured decades earlier. The present study concerns 2,024 breast cancer cases and 1,463 control patients without neoplasms or pathology of the reproductive and digestive organs, seen at Roswell Park Memorial Institute from 1958 to 1965. Based upon the assessments of their varying ingestion of fats from their own reports of diets, no difference in risk was found. Similarly, there was no difference in risk of breast cancer associated with ingesting diets containing various levels of either vitamin C or the cruciferous vegetables. Risk for breast cancer in women 55 yr of age and older increased somewhat with decreases in ingestion of foods containing vitamin A. (Author abstract) (52 Refs)

POSSIBLE IATROGENIC FACTORS IN HUMAN BREAST CARCINOGENESIS

15. A CASE-CONTROL STUDY OF BREAST CANCER AND PSYCHOTROPIC DRUG USE.

Wallace RB, Sherman BM, Bean JA
Dept. Preventive Medicine and Environmental Health, Univ. Iowa, Iowa City, IA, 52242
Oncology; 39(5):279-283 1982

The relative risk of breast cancer incidence and tumor promotion associated with psychotropic drug consumption was evaluated in 151 patients with newly diagnosed neoplasms and 151 hospital controls. No significantly altered risk of breast cancer was found in association with the use of diazepam, chlordiazepoxide, antidepressants, major tranquillizers, sedatives or hypnotics, even after adjustment for known menstrual and reproductive risk factors. No substantial evidence of tumor promotion effects was found, as measured by altered age-at-onset of disease or altered clinical stage at presentation. Psychotropic drug use was inversely related to subject ponderosity (measured by the Quetelet Index) and while this did not confound risk estimates, it may be important in exploring biologic hypotheses of psychotropic drug use and breast cancer. (Author abstract) (28 Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

16. A STUDY ON MAMMARY GLAND TUMORS IN RATS BORN TO PARENTS EXPOSED TO PRECONCEPTION IRRADIATION.

Streltsova VN, Pavlenko-Mikhailov IuN, Oshchepkov AB
No affiliation given
Vopr Onkol; 28(4):45-48 1982

The effect of exposure of male or female rats to radiation 5 days before conception on the frequency of development of mammary tumors in their progeny is described. It was shown that mammary tumor incidence and the rate of their development increase in a population of female rats - descendants of one of parents exposed. Irradiation of would-be mothers produced a stronger blastogenic reaction in their progeny than that of fathers. (Author abstract) (8 Refs) (In RUS)

17. MAMMARY TUMOR INDUCTION IN INBRED MOUSE STRAINS WITH URETHANE IS NOT ACCOMPANIED BY CHANGES IN EXPRESSION OF B- AND C-TYPE RETROVIRAL STRUCTURAL PROTEINS.

Imai S, Morimoto J, Tsubura Y, Hilgers J
Dept. Pathology, Nara Medical Coll., 840 Shijo-cho, Kashihara-shi, Nara-ken 634, Japan
Int J Cancer; 30(1):101-106 1982

Urethane administered in the drinking water of breeding female mice of five inbred strains (DDf, KF, C3Hf, ddY and C57BL) leads to a higher incidence of mammary tumors at an extremely early age in four of these strains (DDf, KF, C3Hf and ddY). In the case of the DDf strain the tumors are adenoacanthomas, but in the case of the other strains adenocarcinomas are also observed. The effect of urethane in the drinking water on expression of endogenous retroviral structural proteins of the B and C type (MTV and MuLV) was studied in the milk by an immunodiffusion test and in organ extracts by radioimmunoassays (for MTVp27, MTVgp52 and MuLVp30). Organs tested include salivary glands, thymus and spleen from female and male animals. In addition, prostate and seminal vesicles were tested in male animals and uterus and mammary glands in females. Mammary tumors induced by urethane were also tested. Urethane does not induce or enhance endogenous retroviral antigen expression, either in these organs or in the mammary gland, one of the target organs for tumorigenesis by this agent. (Author abstract) (34 Refs)

18. FORMATION OF DUCT-ALVEOLAR STRUCTURES AND NEW TYPES OF TUMORS BY A PREGNANCY-DEPENDENT MOUSE MAMMARY TUMOR (TPDMT-4) IN VIRGIN MICE.

Matsuzawa A, Kaneko T, Ikeda Y, Yamamoto T
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Gan; 73(3):372-376 1982

TPDMT-4 tumors showed significant growth in pregnant mice but not in virgins. Tumor pieces at transplant generation 14 were implanted into the gland-free (right) and the intact (left) fat pads in virgin mice and followed over a 1-yr period. The transplants formed outgrowths similar to normal mammary glands in the cleared fat pads. The outgrowths were hyperactive when compared with host glands and varied from one mouse to another in extent of development. In contrast, they did not outgrow and remained as traces among host glands in the intact fat pads. Tumors developed 41 and 32 wk after implantation in the right and the left pads, respectively, in one of 18 mice. The tumor from the cleared fat pad was an ovarian-sensitive pale cell carcinoma, and contained estrogen receptors (ER) but not progesterone receptors (PR). That from the intact fat pad was a type B carcinoma which was ovarian-dependent and contained both ER and PR at levels comparable to those of the parent tumor. (Author abstract) (16 Refs)

19. VARIOUS CHARACTERISTICS OF HORMONE-INDEPENDENCY IN BREAST CANCER (MEETING ABSTRACT).

Kiang DT, Handschin B
Department of Medicine, University of Minnesota Medical School, Minneapolis, MN, 55455
Proc Am Assoc Cancer Res; 23:185 1982

Following serial transplantation, GR mouse mammary tumors transit from hormone-dependent (HD) to -independent (HI). Our previous report indicated that 1) cyclic resurge of progesterone receptor (PgR) occurred every 4-6 generations, even tumors remaining in HI status, and 2) HI tumors in late transplant generations retain low receptor levels. Current study is to assess any qualitative modulation in ER (estrogen receptor) between HD and HI tumors by using IEF (isoelectric focusing) technique, Scatchard plot and by measuring the ability of cytosol-nuclear translocation of receptor-steroid complexes. Four independently developed GR mouse mammary tumor series were used; A, D, E, and F in various transplant generations (generation number in parentheses). Tumors of A(1) through A(4), E(2) and F(2) were HD; while A(5) through A(22) and D(1) were HI. IEF gel analysis revealed a similar single pH 4-5 band in either A(22) HI tumor or E(2) and F(2) HD tumors. During serial transplantations from A(5) through A(13), the quantity of cytosol receptor decreased, while the steroid receptor affinity, Ka steadily increased from 2.2 to 6.5 x 10(9)/M. D(1) tumors had no detectable cytosol ER and PgR.

However, translocation studies revealed that their nuclei had the capability to retain preformed receptor-estradiol complexes. On the contrary, nuclei of A(11) tumors, also HI tumors derived from an initially HD tumor, lost this nuclear binding function. (1 Ref)

20. MAINTENANCE OF OVARIAN-DEPENDENCE OF CARCINOGEN-INDUCED RAT MAMMARY TUMORS SERIALLY-TRANSPLANTED IN PARENCHYMA-CONTAINING MAMMARY FAT PADS (MEETING ABSTRACT).

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Department of Zoology, Michigan State University, East Lansing, MI, 48824

Proc Am Assoc Cancer Res; 23:906 1982

The ovarian-dependent phenotype of carcinogen-induced rat mammary tumors is generally lost following serial transplantation into subcutaneous and intramuscular sites. Accordingly, the purpose of our study was to determine whether the mammary fat pad, the normal site of mammary tumor development, would provide a more favorable environment for the retention of ovarian-dependence. Samples of mammary tumors, induced in Lewis rats by 7,12-dimethylbenz(a)anthracene, were transplanted into syngeneic female hosts, in which the major inguinal mammary fat pads had been either 'cleared' of host mammary parenchyma or were left intact ('uncleared'). In cleared fat pads, transplants of 8 randomly-selected primary mammary tumors gave rise mainly to ductal and hyperplastic outgrowths and rarely to palpable tumors, whereas transplants of 5 ovarian independent tumors consistently formed palpable tumors and no outgrowths. In intact mammary fat pads, transplants from 3 of 6 randomly-selected tumors grew to palpability, and the tumor derivatives of 2 of the 3 tumors were ovarian dependent. One of the ovarian-dependent tumor derivatives was transplanted serially for an additional 5 generations in both intact and cleared fat pads. Consistent growth to palpability and retention of the ovarian-dependent phenotype occurred only in intact fat pads. In contrast, ovarian-independent mammary tumors grew to palpability regardless of whether the fat pad was intact or cleared. (no Refs)

21. LACK OF CORRELATION BETWEEN TRANSFORMED CHARACTERISTICS IN CULTURE AND TUMORIGENICITY OF MOUSE MAMMARY TUMOUR CELLS.

Yates J, King RJ

Cell Biology Div., Glaxo Group Res., Greenford, Middlesex, England

Eur J Cancer Clin Oncol; 18(4):399-403 1982

Androgen responsive and unresponsive Shionogi 115 mouse mammary carcinoma cells have been examined for anchorage-independent growth and tumorigenicity in nude mice. The two cell types exhibit transformed and normal growth characteristics respectively, but both give rise to tumors in nude mice. No correlation between tumorigenicity and transformed characteristics including anchorage-independent growth could be demonstrated. (Author abstract) (11 Refs)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

22. THE EFFECTS OF AGE, REPRODUCTIVE HISTORY AND DMBA DOSE ON THE INDUCTION OF MAMMARY DYSPLASIAS AND TUMORS IN FEMALE C57BL/CRG1 MICE.

Rodriguez RR
University of California, Berkeley, CA
Diss Abstr Int [B]; 42(12,pt1):4709-B 1982

A single dose of 3 mg or 1 mg of 7,12-dimethylbenz(a)anthracene (DMBA) induced a large variety of mammary dysplasias and tumors in female C57BL/Crg1 mice. Because of their morphologic similarities to normal mammary structures, dysplasias were classified as either ductal dysplasias, terminal end bud dysplasias or lobuloalveolar dysplasias. Mammary tumors comprised a separate group and were classified as either malignant, benign or regressed. The kinds of mammary dysplasias and tumors observed were not affected by the age at treatment, or the reproductive history of the treated mice or by the dose of DMBA used. Age at treatment, reproductive history and the dose of DMBA significantly modified the incidences of mammary dysplasias observed. However, dose was the only factor that significantly affected mammary tumor incidences. The emergence of mammary dysplasias and tumors was not affected by any of the three variables. All three classes of mammary dysplasias were recovered as cell dissociation (CD)-derived dysplastic outgrowths both prior to the emergence of overt lesions in donor mice and from donor mice bearing comparable lesions. CD-derived mammary tumors were recovered only from tumor-bearing donors and were only of the malignant type. Reproductive history and the dose of DMBA significantly affected the recovery of CD-derived mammary dysplastic outgrowths. The recovery of CD-derived tumor outgrowths was significantly influenced by age at treatment and the dose of DMBA. (no Refs)

23. INHIBITORY EFFECT OF A FAT-FREE DIET ON MAMMARY CARCINOGENESIS IN RATS.

Davidson MB, Carroll KK
Dept. Biochemistry, Univ. Western Ontario, London, Ontario, N6A 5C1, Canada
Nutr Cancer; 3(4):207-215 1982

Young female Sprague-Dawley rats were administered 7,12-dimethylbenz(a)anthracene, and a wk later the rats were transferred from commerical feed to a semipurified diet containing 20% corn oil. Eight wk after receiving the carcinogen, half of the rats were changed to a fat-free diet to determine the effects on mammary tumor growth and development. After another 20 wk, rats fed the fat-free diet had significantly fewer tumors per tumor-bearing rat and the tumors were smaller than those of rats that continued on the high-fat diet. Rats fed the fat-free diet weighed somewhat less, but showed no physical evidence of essential fatty acid deficiency. Tumors regressed in about half of the rats on the fat-free diet and in some cases became nonpalpable. After 28 wk on this diet, the remaining rats were transferred back to the high-fat diet and subsequently showed a marked stimulation in tumor growth and development. This continued even after the rats were returned to the fat-free diet 8 wk later, indicating that the tumors were no longer susceptible to the deprivation of dietary fat. The results of this study provide further evidence that dietary fat affects the promotional stage of mammary carcinogenesis. (Author abstract) (23 Refs)

24. BREAST TUMORS INDUCED BY N-NITROSOMETHYLUREA (NMU) OR DIMETHYLBENZ(A)ANTHRACENE (DMBA) IN CASTRATED MALES: ROLE OF HIGH FAT DIET (MEETING ABSTRACT).

Rivenson A, Silverman J, Weisburger J
American Health Foundation, Valhalla, NY, 10595
Proc Am Assoc Cancer Res; 23:275 1982

We attempted to extend the findings of Fingerhut and Veenema on the induction of prostate cancer in gonadectomized male Fischer F-344 rats on 20% and 5% fat diets, utilizing iv dosing with 7,12-dimethylbenz(a)anthracene (DMBA), and also 2',3-dimethyl-4-aminobiphenyl (DMAB), and N-nitrosomethylurea (NMU). No prostate cancers were found in rats held for 68 weeks. However, with NMU and DMAB these gonadectomized male rats had breast cancers in a higher incidence on the 20% fat diet with NMU but not with DMAB. All neoplasms were malignant, with invasion and destruction of neighboring tissues, and presenting histologically mixed glandular and squamous structures, quite distinct from lesions usually seen in females. Similar type of adeno-squamous carcinomas could be seen in tumors of the ear duct (Zymbal glands) and bulbo urethral glands developed in rats given the above carcinogens. The topographic location of the tumors labeled grossly as 'breast tumors' excluded other possible similar glandular structures and also a sweat gland tumor since the rat skin does not contain sweat glands. Other tumors noted after the carcinogens given iv were: bladder, DMAB only; small intestine and colon, NMU and DMAB; lung, DMBA, NMU, and DMAB; sc sarcoma, NMU and DMAB; stomach NMU. Several of these cancers exhibited metastases. None of the tumors noted above were present in controls. In summary, NMU and DMAB induced tumors in a number of sites, but selectively caused mammary gland adenocarcinoma and adenosquamous carcinoma, and Zymbal gland adenoepidermoid carcinoma. (1 Ref)

25. ALTERATION IN DNA-DEPENDENT RNA POLYMERASE ACTIVITY BY RETINOIDS (MEETING ABSTRACT).

Mehta RG, Cerny WL, Moon RC
Life Science Division, Illinois Institute of Technology, Chicago, IL, 60616
Proc Am Assoc Cancer Res; 23:82 1982

Although the inhibitory effect of retinoids against chemically-induced mammary carcinogenesis in rats is well established, very little is known about the mechanism through which these effects are mediated. Earlier we reported the presence of retinoic acid binding proteins in the cytosol (cRABP) of carcinogen-induced mammary tumors. These components sedimented in the 2S region when analyzed by sucrose density gradient centrifugation. Furthermore, under appropriate conditions retinoic acid bound cRABP complex interacts with nuclei isolated from these tumors; RABP isolated from nuclei also sedimented as a 2S component. We now have extended these studies to determine if the mammary tumor RABP has any functional role in alteration of DNA dependent RNA polymerase activity in the nuclei. RNA polymerase activity was measured as incorporation of [3H]uridine monophosphate into trichloroacetic acid precipitable material. Cytosol containing 3.7pmoles of RA-cRABP complex (130ug protein), preformed by incubating 1uM unlabeled retinoic acid with tumor cytosol at 4C for 16 hr in dark, inhibited RNA polymerase I activity in mammary tumor nuclei by 35%. Under similar conditions, 1uM unbound RA had no effect. Mammary tumor nuclei which were incubated with cytosol containing RA-cRABP complex for 30 min at 25C also reduced Mg dependent RNA polymerase activity by over 70% compared to the nuclei preincubated with buffer under identical conditions. There was no significant influence of the RABP complex on Mn dependent RNA polymerase activity. (no Refs)

26. INHIBITION OF CARCINOGENESIS OF THE RAT MAMMARY GLAND AND MOUSE URINARY BLADDER BY A RETINOID AND AN INDUCER OF INTERFERON SYNTHESIS (MEETING ABSTRACT).

McCormick DL, Becci PJ, Moon RC
Illinois Institute of Technology Research Institute, Chicago, IL, 60616
Proc Am Assoc Cancer Res; 23:354 1982

Retinoids are potent inhibitors of chemical carcinogenesis of the mammary gland and urinary bladder in experimental animals. MVE-2 is a divinyl ether-maleic anhydride copolymer which induces interferon synthesis. These studies were conducted to determine the influence on chemical carcinogenesis of combined administration of MVE-2 and the retinoid N-(4-hydroxyphenyl)retinamide (4-HPR). In the mammary study, virgin female Sprague-Dawley rats received a single iv dose of 20 mg N-methyl-N-nitrosourea per kg body weight. In the bladder study, male C57BL/6 x DBA-2 F1 mice received 8 weekly ig doses of 7.5 mg (4-(butylnitrosoamino)-1-butanol). One week after the final carcinogen treatment, animals in both studies were randomized into groups of 50 as follows: (1) placebo diet (2) 4-HPR, 391 mg/kg diet (3) MVE-2, 25 mg/kg body weight, administered ip in 4 week cycles (3 weeks treatment, 1 week rest) throughout the study (4) MVE-2, 12.5 mg,kg, given as above (5) 4-HPR diet +— 25 mg MVE-2/kg (6) 4-HPR diet + 12.5 mg MVE-2/kg. In both studies, 4 HPR (group 2) and the high dose MVE-2 (group 3) treatments resulted in a significant inhibition of carcinogenesis. The low dose of MVE-2 (group 4) was not active in chemoprevention. No synergistic or additive interaction was observed between 4-HPR and MVE-2 at either dose level. These data suggest that either 4-HPR and MVE-2 inhibit carcinogenesis by a common mechanism, or, more likely, that the compounds have an antagonistic activity which precludes an additive or synergistic interaction in cancer inhibition. (no Refs)

27. RETINOID FEEDING, HORMONE INHIBITION AND/OR IMMUNE STIMULATION AND THE GENESIS OF DMBA-INDUCED RAT MAMMARY TUMORS (MEETING ABSTRACT).

DeHoog JV, Welsch CW
Department of Anatomy, Michigan State University, East Lansing, MI, 48824
Proc Am Assoc Cancer Res; 23:341 1982

Two groups of 320 female Sprague-Dawley rats were treated ig with 20 mg (series I) or 10 mg (series II) of 7,12-dimethylbenzanthracene (DMBA) per rat at 50 days of age. At 53 days of age each series was divided into 8 groups of rats (40 rats/group), ie, (1) controls (C), (2) immunestimulated (IS), (3) hormone inhibited (HI), (4) HI+IS, (5) retinoid fed (RA), (6) RA+IS, (7) RA+HI, (8) RA+HI+IS. HI - Tamoxifen (25 ug/100 g body wt) and 2-Br-alpha-ergocryptine (CB-154) (400 ug/100 g body wt) injected sc once daily. IS - Norcardia rubra (1 mg/rat) injected sc once weekly (series I) or methanol extracted residue (MER) of Bacillus Calmette-Guerin (BCG) (0.5 mg/rat) injected ip at 3 and 5 weeks after DMBA treatment (series II). RA - retinyl acetate, fed daily, 0.2 mM/kg ration (series I) and 0.6 mM/kg ration (series II). Groups 1,2,5 and 6 were sacrificed 12 weeks after DMBA treatment; groups 3,4,7 and 8 at 20 weeks post carcinogen. Mammary tumor incidence was significantly reduced in rats treated with HI or fed a moderate dose of RA. Tumor incidence was further reduced in HI treated rats fed either a moderate or low dose of RA; low dose of RA alone was ineffective. IS alone or in combination did not influence this neoplastic process. (no Refs)

28. DAUNORUBICIN (D) INDUCED MAMMARY TUMORS IN FEMALE SPRAGUE-DAWLEY RATS AND THE ROLE OF ALPHA-TOCOPHEROL (ALPHAT) AS A MODIFIER TO THE CARCINOGENESIS (MEETING ABSTRACT).

Wang YM, Howell SK, Tsai CC, Van Eys J
M. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030
Proc Am Assoc Cancer Res; 23:352 1982

Second malignancies are significant side effects of cancer chemotherapy. Anthracycline antibiotics-induced tumors have been recognized in rats and monkey. We have, recently, investigated the activity of alphaT as a potential modifier to the carcinogenecity-induced by D in female rats. Two groups of rats at age 40 day (less than 125 g) and 48-56 days (150-200 g) respectively were used. In older animals, D (10 mg/kg) injected intravenously induced tumors in 50% (11/22) of the animals. Preinjection with alpha-tocopheryl acetate (alphaTA, 300 mg/kg/day) daily for consecutive 4 days prior to the injection of D reduced significantly the tumor incidence (2/16). In younger animals, tumor incidence was less (5/21) and the pretreatment with the vitamin did not modify the tumor development (9/27). In older animals, organ distribution of 3H-D and 14C-alphaTA changes by each other, however, alphaTA does not alter the concentration of D in mammary tissue and fat. However, in single mammary epithelial cells suspensions isolated in rats after 4 daily treatment of alpha-TA or placebo, the intracellular D distribution was significantly modified in the presence of alphaT and alphaTA. The concentration of 3H-D in nuclear fractions was 30-40% in those cells isolated from alphaT treated animals as compared to the cells from placebo treated animal. It appears the alteration of subcellular D distribution by the vitamin may play a role in the modification of D-induced mammary tumor in rats. (no Refs)

29. EFFECTS OF ARGININE ON THE CARCINOGENICITY OF N-METHYL-N-NITROSOUREA (MNU) AND 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA) (MEETING ABSTRACT).

Burns RA, Milner JA
Department of Food Science, University of Illinois, Urbana, IL, 61801
Proc Am Assoc Cancer Res; 23:271 1982

Female Sprague-Dawley rats were used to investigate the effects of dietary arginine on the occurrence of mammary tumors induced by DMBA and MNU. Sixty rats were fed either a control 14% casein diet or the same diet supplemented with 5% arginine starting at 36 days of age. At 50 days of age, 30 rats from each treatment were intubated intragastrically with 7.5 mg DMBA in sesame oil. The remaining 30 in each treatment were given MNU (40 mg/kg body weight) via the jugular vein. Mammary tumors were detected by weekly palpation from 5-18 weeks after carcinogen administration. Dietary arginine supplementation did not alter food intake or weight gain. Total palpable mammary tumors for each group increased at a linear rate. For DMBA-treated rats the rate was 8.1 new palpable tumors per week for controls compared to 4.7 for arginine-supplemented rats. The respective rates were 8.9 and 6.8 tumors/week for MNU-treated rats. In DMBA-treated rats the time for 50% of the rats to develop tumors was increased from 9.3 to 12.5 weeks by dietary arginine supplementation, whereas in MNU-treated rats this time was not affected by arginine. Eighteen weeks after DMBA, 23 control and 21 arginine-supplemented rats had tumors and after MNU the corresponding numbers were 27 and 23. The greater inhibition by arginine of DMBA- than MNU-induced tumor formation indicates that arginine may inhibit the activation of procarcinogens (DMBA). (no Refs)

30. INHIBITION OF PHORBOL ESTER ENHANCEMENT OF MOUSE MAMMARY TUMOR VIRUS PRODUCTION BY ANTI-GLUCOCORTICOIDS (MEETING ABSTRACT).

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Department of Biomedical and Environmental Health Sciences, University of California, Berkeley, CA, 94720
In Vitro; 18(3,part2)·309 1982

Production of mouse mammary tumor virus (MMTV) is known to be significantly enhanced by glucocorticoid hormones in infected cell cultures. More recently, it has been shown that the tumor promoting phorbol ester, 12-O-tetradecanoylphorbol-13-acetate (TPA), can also stimulate MMTV production. In this investigation, four compounds, deoxycorticosterone, 11-deoxycortisol, 17alpha-methyltestosterone and progesterone were shown to be have anti-glucocorticoid activity as determined by their ability to antagonize the stimulation of MMTV production by dexamethasone in Mm5mt cells. All four of these anti-glucocorticoids also proved to be effective in antagonizing TPA-induced enhancement of MMTV production, as measured by a RNA-dependent DNA polymerase assay. (no Refs)

31. EFFECTS OF AROMATASE INHIBITOR 4-HYDROXYANDROSTENEDIONE AND OTHER COMPOUNDS IN THE 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED BREAST CARCINOMA MODEL.

Brodie AM, Garrett WM, Hendrickson JR, Tsai-Morris CH
Dept. Pharmacology and Experimental Therapeutics, Univ. Maryland Sch. Medicine, Baltimore, MD, 21201
Cancer Res; 42(8,Suppl):3360s-3364s 1982

Aromatase inhibitor, 4-hydroxyandrostene-3,17-dione (4-OHA), is a highly effective treatment in rats with 7,12-dimethylbenz(a)anthracene-induced hormone-dependent mammary tumors. Over 90% of tumors regress to less than one-half of their original size, and a high proportion regress completely. Treatment of rats with other inhibitors, 4-acetoxyandrostene-3,17-dione and 1,4,6-androstatriene-3,17-dione produce similar results. In comparison with other aromatase inhibitors, the compounds reduced ovarian estrogen secretion in the rat to the same extent as aminoglutethimide, whereas Teslac was without effect. The latter two compounds caused little and no regression of DMBA-induced mammary tumors, respectively. Our recent studies with 4-OHA, 4-acetoxyandrostene-3,17-dione, and 1,4,6-androstatriene-3,17-dione indicate that they interact with aromatase by a two-component mechanism, a rapid competitive inhibition, and a slower enzyme inactivation. Treatment of rats with 4-OHA also caused greater than 80% loss of ovarian aromatase activity in vivo and a reduction in ovarian estrogen secretion, which are maintained for at least 48 hr after injection. Although 4-OHA is cleared rapidly in vivo, the above results suggest that the compound has a sustained effect. Thus, when 7,12-dimethylbenz(a)anthracene-induced tumor-bearing rats were treated with 4-OHA injections on alternate wk, tumor regression continued to occur during wk without treatment. The overall regression was similar to that with continuous treatment. 4-OHA is also effective and similar to ovariectomy in rats with hormone-dependent metastatic mammary tumors produced by nitrosomethylurea. Our results indicate that mammary tumor regression induced by 4-OHA is mainly the result of the inhibition of aromatization, although other activities of the compound may also contribute. (Author abstract) (23 Refs)

32. EFFECT OF AN AROMATASE INHIBITOR, 1,4,6-ANDROSTATRIENE-3,17-DIONE, ON 7,12-DIMETHYLBENZ[A]ANTHRACENE-INDUCED MAMMARY TUMORS IN THE RAT AND ITS MECHANISM OF ACTION IN VIVO.

Brodie AM, Brodie HJ, Garrett WM, Hendrickson JR, Marsh DA, Tsai-Morris CH
Dept. Pharmacology and Experimental Therapeutics, Univ. Maryland Sch. Medicine, 660 W. Redwood St., Baltimore, MD, 21201
Biochem Pharmacol; 31(11):2017-2023 1982

In this study, 1,4,6-androstatriene-3,17-dione (ATD) was demonstrated to cause time-dependent loss of aromatase activity in rat ovarian microsomes in vitro. In vivo, an injection of ATD caused inhibition of ovarian aromatase and reduced estrogen secretion in pregnant mare's serum gonadotropin-primed rats for at least 24 hr after injection. In rats with 7,12-dimethylbenz[a]anthracene-induced, hormone-dependent, mammary tumors, marked regression occurred with ATD treatment. Although estrogen secretion was not reduced below the diestrus level of controls, the rats remained anestrus, indicating that the proestrus surge of estrogen was prevented. LH, FSH and prolactin levels were also basal and LH and FSH did not rise after ovariectomy. ATD had no detectable hormonal activity in bioassay. Consistent with this, the compound did not interact appreciably with either androgen or estrogen receptors, was not uterotrophic, and did not interfere with mammary tumor regression in ovariectomized rats. Thus, the major activities of the compound which cause mammary regression in the rat appear to be inhibition of estrogen synthesis, via aromatase and gonadotropin suppression. (Author abstract) (24 Refs)

33. MISLETOE PREPARATIONS PREVENT CHANGES IN COPPER METABOLISM WHICH NORMALLY OCCUR IN RATS WITH IMPLANTED TUMORS (MEETING ABSTRACT).

Linder MC, Murillo C
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Proc Am Assoc Cancer Res; 23:18 1982

The presence of malignant tumors in rats and man causes several clear cut changes in the copper metabolism of the host, including increases in plasma Cu and ceruloplasmin (CP) concentrations, increased synthesis of CP, enhanced intestinal Cu absorption, decreased turnover of total body Cu, and decreased concentrations of Cu in liver and kidney. Iscador (ISC) is an anticancer drug prepared from the mistletoe, and used in some European countries. We have applied it as a first step in assessing the effects of anticancer drugs on Cu metabolism. ISC (mali, 5%) (0.05-0.30 ml per rat) was injected intraperitoneally, daily, into adult rats with and without subcutaneous tumors, from the day of implantation. Tumors used were the fast-growing, undifferentiated Dunning mammary tumor DMBA-5A, and Morris hepatomas 5123tc and 7777. ISC had no obvious effects on normal rats and their Cu metabolism. However, in rats with tumors there was a striking effect on some parameters. Even with very large tumors, tumor-bearing rats with ISC retained nearly normal hematocrits and liver Cu concentrations, as compared with decreases of 20-30% in the untreated rats. Plasma Cu and CP were also closer to normal. Although tumor growth rates (in volume) were not significantly depressed with ISC, tumor viability was much less, as judged by gross dissection. The results are compatible with the concept that alterations of Cu metabolism are factors which underlie the successful progression of the cancer process. (no Refs)

34. EFFECT OF HIGH-DOSE OESTROGEN ADMINISTRATION ON THE GROWTH AND PROLACTIN RECEPTOR CONTENT OF N-NITROSOMETHYLUREA-INDUCED MAMMARY TUMOURS IN THE RAT.

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J Endocrinol; 93(1):11-16 1982

The effect of chronic administration of a high dose of estradiol benzoate (OB) on growth and prolactin receptor content of the N-nitrosomethylurea (NMU)-induced rat mammary tumor was investigated. Daily im administration of 50 ug OB for 8 days to tumor-bearing rats induced marked reduction in tumor size which was already significant after only three injections. Simultaneous daily administration of 1 mg perphenazine to stimulate endogenous prolactin release counteracted the inhibitory effect on tumor growth of OB but only partially since the tumors grew significantly more when perphenazine was injected alone. No treatment significantly affected prolactin receptor content in the tumors. We concluded that administration of pharmacological doses of OB has a potent antitumor action on the NMU-induced rat mammary tumor. This effect can only partially be explained by inhibition of the peripheral action of prolactin. (Author abstract) (22 Refs)

35. EFFECT OF OVARIECTOMY AT DIFFERENT AGES ON THE INCIDENCE OF 7,12-DIMETHYLBENZ(A)ANTHRACENE-INDUCED MAMMARY HYPERPLASTIC ALVEOLAR NODULES IN FEMALE RATS.

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(c/o Toh) Dept. Physiology, Univ. New England, Armidale, New South Wales 2351, Australia
IRCS Med Sci [Cancer]; 9(9):778 1981

The effect of ovariectomy at birth on the incidence of mammary hyperplastic alveolar nodules in female rats was compared with ovariectomy performed at 28 and 114 days of life. The incidence of hyperplastic alveolar nodules was significantly decreased in mammary glands of female rats following ovariectomy at day 1 and 28 when compared with the respective sham-operated groups. Ovariectomy performed at day 114 showed very little effect on the mammary noduligenesis. Ovariectomy at birth produced the greatest effect. (5 Refs)

36. ACCELERATED DEVELOPMENT OF SPONTANEOUS AND BENZOPYRENE-INDUCED SKIN CANCER IN MICE EXPOSED TO 2450-MHZ MICROWAVE RADIATION.

Szmigielski S, Szudzinski A, Pietraszek A, Bielec M, Janiak M, Wrembel JK
Dept. Biological Effects Non-ionizing Radiation, Center for Radiobiology and Radioprotection, 128 Szaserow, 00-909 Warsaw, Poland
Bioelectromagnetics; 3(2):179-191 1982

Microwave (MW; 2,450-megahertz) treatment for 1-6 mo, of C3H/HeA (CA) mice with high incidence of spontaneous breast cancer and of Balb/c mice with skin cancer induced with topical benzo(a)pyrene (BP), resulted in significant acceleration of tumors. Mice were exposed to MWs in an anechoic chamber at 5 or 15 milliwatts (mW)/square cm (cm2) 2 hr/day x 6/wk. CA mice were irradiated from wk 6 of life up to mo 12. Balb/c mice treated with BP were irradiated either prior to (over 1 or 3 mo) or simultaneously with BP treatment (over 5 mo). Two additional groups were exposed to chronic stress (caused by confinement) or to sham-irradiation; these groups served as controls. The acceleration of tumor growth was accompanied by lowering of the natural antineoplastic resistance as measured by the number of cancer colonies in the lung, which occurred whether MWs were applied before or simultaneous with BP. The acceleration of cancer development in all tested systems and lowering of antineoplastic resistance was similar in mice exposed to MW at 5 mW/cm2 or to chronic stress but differed significantly from the data obtained on animals exposed at 15 mW/cm2, where local thermal effects ('hot' spots) were possible. It is concluded that under the tested experimental conditions, long-term exposure to MW fields may be a potential carcinogenic risk factor. (15 Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

37. ENDOGENOUS HORMONES AS A MAJOR FACTOR IN HUMAN CANCER.

Henderson BE, Ross RK, Pike MC, Casagrande JT
Dept. Family and Preventive Medicine, Univ. Southern California Sch. Medicine, Los Angeles, CA, 90033
Cancer Res; 42(8):3232-3239 1982

Hormone-related cancers account for almost 30% of all cancer cases in the United States. Data from animal experiments and from epidemiological and endocrinological studies in humans support the hypothesis that the individual hormones which control normal growth of target organs can also create the proper conditions for neoplastic transformation. The concept that hormones can cause, ie, increase the incidence of, human cancer is most developed for the four hormone-related cancers which are numerically the most important, namely, breast, prostate, endometrium, and ovary. Even for these sites, large gaps remain in our knowledge of the responsible hormones and the conditions which create the optimal opportunity for carcinogenesis. Although scanty, the available epidemiological evidence also suggests a hormonal role in the pathogenesis of testis cancer, thyroid cancer, and osteosarcoma. We believe that the primary prevention of all these cancers will probably depend on modification of the factors which affect the secretion and metabolism of the responsible hormones rather than on control of exposure to classical exogenous initiators. (Author abstract) (129 Refs)

38. URINARY OESTROGENS AND PREGNANDIOL IN BREAST CANCER PATIENTS.

Zaki K, El-Kharadly M, El-Faras A, Nour H, Kamel NI
Dept. Physiology, Medical Res. Inst., Alexandria Univ., Alexandria, Egypt
Endokrinologie; 79(1):49-56 1982

Urinary E1, E2, E3 and pregnandiol was determined in 60 premenopausal and 12 postmenopausal breast cancer patients before and after mastectomy, as well as in 30 normal females. Data obtained showed great individual variation. The general findings were low estrogens in young patients, normal in old premenopausal patients and high in post-menopausal patients. The ratio E3/E1 + E2 showed comparatively high values in premenopausal patients. Pregnandiol excretion was low in almost all premenopausal patients with the exception of few cases in the different age groups. The changes in the hormonal pattern in premenopausal breast cancer patients, before and after mastectomy, and of postmenopausal patients were discussed in view of the current literature. (Author abstract) (23 Refs)

39. URINARY ANDROGEN METABOLITES AND RECURRENCE RATES IN EARLY BREAST CANCER.

Thomas BS, Bulbrook RD, Hayward JL, Millis RR

Imperial Cancer Res. Fund, P.O. Box 123, London WC2A 3PX, England

Eur J Cancer Clin Oncol; 18(5):447-451 1982

Androsterone and aetiocholanolone was measured in urine specimens obtained from 218 women with early breast cancer. Patients who excreted less than the median amount of these steroids had a significantly higher recurrence rate (p less than 0.005) than patients excreting more than the median value. The relationship between androgen excretion and recurrence is stronger in pre-menopausal women than in the post-menopausal group. The androgen assays are still associated with recurrence rates when patients are stratified by pathological stage, but no clear relationship was found with histological grade. (Author abstract) (23 Refs)

40. CONCENTRATION OF ENDOGENOUS OESTRADIOL AS RELATED TO OESTRADIOL RECEPTOR SITES IN BREAST TUMOR CYTOSOL.

Thorsen T, Tangen M, Stoa KF

Hormone Lab., Univ. Bergen Sch. Medicine, Bergen, Norway

Eur J Cancer Clin Oncol; 18(4):333-337 1982

Biopsies or mastectomy specimens from 26 malignant and 17 non-malignant human breast tumors have been examined with respect to cytoplasmic estradiol receptors and endogenous estradiol concentration. Of the malignant tumors, 45 (65%) had significant estradiol receptor concentrations (136.7 fmol/mg protein +-38.3 SEM). Estradiol values in the cytosol were not correlated to receptor levels. Cytosol estradiol concentrations in the receptor-negative tumors were normally distributed about a mean value of 7.4 fmol/mg protein +-0.9 (SEM). Estradiol levels were similar to the median concentration of receptor found in tumors from younger women, and consequently may influence receptor measurements in such tumors. In receptor-positive cytosols a much wider range (less than 1 to 69.7 fmol/mg protein) and a non-symmetrical distribution of estradiol values were found which closely corresponded to the range of occupied receptor concentrations previously measured in tumor cytosol. When tumors have undetectable estradiol values were excluded, receptor-positive cytosols had significantly higher estradiol concentrations than those found in receptor-negative tumors (p less than 0.01). No significant difference in cytosol estradiol concentration was found in receptor-positive and negative pre- and postmenopausal women. This would indicate that factors other than plasma levels influence tissue availability of estradiol. (Author abstract) (29 Refs)

41. CYTOLOGICAL STUDY ON THE ANTERIOR PITUITARY OF SENILE UNTREATED BEAGLE BITCHES WITH SPONTANEOUS MAMMARY TUMOURS.

Attia MA

Drug Safety R and D Lab., Organon International B.V., P.O. Box 20, Oss, The Netherlands

Arch Toxicol; 50(1):35-45 1982

Pituitaries were obtained from senile untreated Beagle bitches of comparable age (7-9 yr) and genital status. The animals were divided into three groups; one was normal (without mammary lesions), one had benign tumors and one had mammary adenocarcinomas. PRL-, STH-, ACTH- and gonadotrophin-producing cells are studied and counted in serial paraffin sections stained with histochemical techniques. The animals with mammary malignancy displayed a marked increase in the relative number of PRL and ACTH cells with morphological signs of higher secretory activity in most cells, compared with that in normal bitches or bitches with benign tumors. STH cells in bitches with adenocarcinomas were reduced in number; however the secretory activity in these animals was the same as that observed in the normal bitches. In the animals with benign mammary tumors, STH cells showed morphological indication of higher secretory activity than in the other groups. PRL and ACTH cells were slightly increased in number and had slightly higher activity than that in normal bitches. These findings may suggest a role for hypophyseal hormones in mammary neoplasias. (Author abstract) (18 Refs)

42. ENHANCED AND REVERSED GROWTH IN VIVO OF A PREGNANCY-DEPENDENT MOUSE MAMMARY TUMOR (TPDMT-4) BY A GONADOTROPIN-RELEASING HORMONE AGONIST ANALOG.

Matsuzawa A, Yamamoto T

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Eur J Cancer Clin Oncol; 18(5):495-505 1982

TPDMT-4 pregnancy-dependent mammary tumors grow continuously in DDD female mice carrying pituitary isografts (PI) ectopically or bearing an sc 17beta-estradiol plus progesterone (EP) pellet. A gonadotropin-releasing hormone (GnRH) agonist (D-leucyl6, des-glycyl-NH210, prolyl-ethylamide9) GnRH (TAP-144), was examined for its antitumor activity in these experimental systems. TAP-144 was injected ip at doses of 300 and 600 ug 6x weekly, when tumors grew to significant sizes. TAP-144 enhanced tumor growth during the first 2 weeks and subsequently reversed it in a dose-related manner in PI-bearing mice. The agonist did not affect tumor growth in the absence of ovaries in these mice. In ovariectomized mice, TAP-144 enhanced EP pellet-induced tumor growth but never reversed it. In ovariectomized, PI-bearing mice. TAP-144 first enhanced and subsequently reversed tumor regrowth induced by ovarian grafts to a greater extent when commencing it simultaneously with ovarian grafting than 30 days before it. The agonist also exerted the dual effects on TPDMT-4V ovarian-dependent subline tumors in the absence of PI. In TAP-144-treated mice, enhanced tumor growth was related to many solid corpora lutea in ovaries and fully developed mammary glands, but reversed growth was related to atrophied luteal components and mammary glands. The results suggest that TAP-144 enhances tumor growth first via its stimulative action on the pituitary-ovarian axis and causes tumor regression later via its direct inhibitory action on ovaries. (Author abstract) (31 Refs)

43. RADIOTRACERS BINDING TO ESTROGEN RECEPTORS: I: TISSUE DISTRIBUTION OF 17 ALPHA-ETHYNYLESTRADIOL AND MOXESTROL IN NORMAL AND TUMOR-BEARING RATS.

Feenstra A, Nolten GM, Vaalburg W, Reiffers S, Woldring MG

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J Nucl Med; 23(7):599-605 1982

Ethynylestradiol and moxestrol can be labeled with carbon-11 by introducing this positron emitter in the 17alpha-ethynyl group. To investigate their potential as radiotracers binding to estrogen receptors, we studied the tissue distribution of tritiated ethynylestradiol and moxestrol, with specific activities of 57 Ci/mmol and 77-90 Ci/mmol, respectively, in the adult female rat. At 30 min after injection, both compounds showed specific uptake in the uterus (% dose/g): 2.52 for ethynylestradiol and of 2.43 for moxestrol. A decrease of the specific activity to 6-9 Ci/mmol resulted in uterine uptakes of 1.60 and 2.10 respectively, for ethynylestradiol and moxestrol, at 30 min. In the female rat bearing DMBA-induced mammary tumors, specific uptake was also measured in the tumors, although the values were only 25-30% of the uterine uptake. Moxestrol showed a greater uptake selectivity in the tumors compared with ethynylestradiol. From this study we conclude that ethynylestradiol and moxestrol have good potential as tracers binding to mammary tumors that contain estrogen receptors. (Author abstract) (24 Refs)

44. STEROID HORMONE RECEPTORS IN THE RAT MAMMARY ADENOCARCINOMA INDUCED BY N-HYDROXY-N-2-FLUORENYLACETAMIDE.

Li SA, Malejka-Giganti D, Li JJ

Medical Res. Lab., Veterans Admin. Medical Center, Minneapolis, MN, 55417

JNCI; 69(1):41-45 1982

The steroid hormone receptors in N-2-fluorenylacetamide (2-FAA)- and N-hydroxy-2-FAA-induced mammary adenocarcinomas in outbred Sprague-Dawley rats were analyzed. Both 8S and 4S estrogen-binding components have been detected in cytosols of these tumors following sucrose gradient sedimentation in low salt. Competitive binding analyses of this binder indicated a specificity profile expected of an estrogen receptor. Both androgen and progesterone receptors were also present in the cytosols of these mammary tumors. While the androgen receptor sedimented in the 8S region of the gradient, the progestin binder appeared only as a 4S moiety under similar conditions. The relative concentrations of these receptors (expressed in fmol/mg protein +- SE) were: 17 beta-estradiol (28.6 +-4.1) greater than 5alpha-dihydrotestosterone (8.5 +-2.2) greater than progesterone (5.0 +-1.3). The progesterone receptor was increased at least eightfold in the mammary adenocarcinomas from ovariectomized rats that were treated with diethylstilbestrol for 6 days. Binding equilibrium data indicated K = 1.2-1.8 x 10(9) M-1 for the above cytoplasmic hormone receptor complexes (Ka, association constant). Although cytosols prepared from lactating mammary gland contained appreciable quantities of glucocorticoid receptor, only trace amounts were found in the mammary adenocarcinoma. (Author abstract) (33 Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

45. IMMUNE ALTERATIONS RELATED TO AGE AND MAMMARY TUMOR DETECTION IN C3H/BI MICE.

Dufer J, Benoist H, Bouchet C, Desplaces A, Saracino RT
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Bull Cancer (Paris); 69(2):143-148 1982

The immune status of C3H/Bi mouse, a strain characterized by its high incidence of spontaneous mammary tumors, has been evaluated before and after palpable tumor detection. Spleen cells were studied in vitro: phytohemagglutinin (PHA) stimulation and antibody dependent cellular cytotoxicity (ADCC). Immune responses against sheep red blood cells, lipopolysaccharide and oxazolone were evaluated in vivo. Three mice groups were defined: 2-4 mo old mice without tumor - at that age, tumor frequency was near zero; 5-6 mo old mice, without palpable tumor - in this group, tumor appearance was very near, since 8-9 mo old mice showed a tumor frequency of 90-95%; tumor-bearing mice, more than 5 mo old. As compared to 2-4 mo old mice, 5-6 mo old mice without tumor showed an enhanced PHA stimulation of splenocytes and a decreased ADCC response. In addition, in vivo immune response to sheep red blood cells was decreased whereas other responses were unchanged. On the other hand, immune responses of tumor bearing mice did not differ from those of 2-4 mo old mice, both in vivo and in vitro. These data suggest a variation of immunological parameters in C3H/Bi mice, both in terms of age and of spontaneous mammary tumor appearance. (Author abstract) (15 Refs) (In FRE)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

46. IDENTIFICATION OF A UNIQUE MOUSE MAMMARY TUMOR VIRUS IN THE BALB/CNIV MOUSE STRAIN.

Puma JP, Fanning TG, Young LJ, Cardiff RD
Chiron Corporation, Berkeley, CA, 95616
J Virol; 43(1):158-165 1982

We examined the genetic structure, in terms of restriction endonuclease recognition sites, of the milk-transmitted, low-oncogenic mouse mammary tumor virus (MuMTV) of the BALB/cNIV mouse strain. An analysis with EcoRI documented the presence of acquired cNIV proviruses in the mammary tumor DNAs of BALB/cNIV animals. A comparison of tumor DNAs digested with PstI showed that both the cNIV MuMTV and C3Hf MuMTV proviruses lacked the 4.3-and 1.1-kilobase pair fragments characteristic of C3H MuMTV patterns. An examination of mammary tumor and normal, nonmammary tissue DNAs with BamHI supported the idea that the cNIV MuMTV is identical to the C3Hf MuMTV and demonstrated that these two low-oncogenic proviruses are identical to the high-oncogenic C3H MuMTV provirus with respect to a pair of BamHI sites which define a 1.3-kilobase pair fragment. For each of the three MuMTV strains, we also mapped DNAs generated in isolated virions by reverse transcription of their genomic RNAs. Our results showed that cNIV and C3Hf MuMTV are distinct entities by virtue of an additional PstI site within the cNIV long terminal repeat sequence. Another unique feature of cNIV MuMTV revealed by the analysis of virion-generated DNAs was the existence of a family of genomes within the cNIV population. We concluded that cNIV is distinct from its presumptive C3Hf MuMTV predecessor. (Author abstract) (26 Refs)

47. DETECTION OF ACQUIRED PROVIRUS SEQUENCES IN MAMMARY TUMORS FROM LOW-EXPRESSOR, LOW-RISK MICE.

Altrock BW, Cardiff RD, Puma JP, Lund JK
(c/o Cardiff) Dept. Pathology, Sch. Medicine, Univ. California, Davis, Davis, CA, 95616
JNCI; 68(6):1037-1041 1982

Murine mammary tumor virus (MuMTV) provirus sequences in the DNA from early-occurring (av age 10 mo) and late occurring (age greater than 20 mo) tumors in BALB/cfC3H mice were analyzed by Eco RI restriction endonuclease mapping procedures. All early tumors were MuMTV antigen-positive mammary adenocarcinomas that contained the 0.92-and 4.0-kilobase (kb) exogenous C3H MuMTV-specific Pst I restriction endonuclease fragments. All but one of the late mammary adenocarcinomas had MuMTV antigens detected by peroxidase antiperoxidase staining, and all contained the 0.92-and 4.0-kb exogenous virus Pst I fragments. Three late nonmammary tumors lacked both MuMTV antigens and acquired provirus sequences. Greater numbers of MuMTV sequences were detected in both early and late-arising mammary tumors by Eco RI restriction endonuclease mapping than were detected in tissues from uninfected BALB/c mice. However, neither the number nor the location of MuMTV proviruses correlated with tumor latent period. (Author abstract) (19 Refs)

48. NOVEL CLASS OF MOUSE MAMMARY TUMOR VIRUS-RELATED DNA SEQUENCES FOUND IN ALL SPECIES OF MUS, INCLUDING MICE LACKING THE VIRUS PROVIRAL GENOME.

Callahan R, Drohan W, Gallahan D, D'Hoostelaere L, Potter M
Lab. Cellular and Molecular Biology, NCI, NIH, Bethesda, MD, 20205
Proc Natl Acad Sci USA; 79(13):4113-4117 1982

Mice in breeding colonies of feral Mus musculus brevirostris (Azrou, Morocco), M m musculus (Studenec, Czechoslovakia), and M m molossinus (Fukuoka, Japan) were found to lack the mouse mammary tumor virus (MMTV-alpha) proviral genome in their germ line. MMTV-alpha proviral genomes have been found in all inbred strains of M musculus by using high-stringency nucleic acid hybridization conditions. We conclude that feral mice in these colonies are heterozygous for a limited number of MMTV-alpha proviral genomes and that those lacking them arose as a result of random chromosomal segregation. All mice in another breeding colony of feral M m musculus (Sladeckovce, Czechoslovakia) lack MMTV proviral genes. By relaxing the conditions of nucleic acid hybridization, MMTV-related sequences (designted MMTV-beta) were detected in restricted cellular DNA from MMTV-negative mice and all other inbred strains and feral species of the genus Mus. The apparent ubiquity of the MMTV-beta DNA sequences in the genus Mus and the lack of variation in the pattern of restriction fragments containing these sequences within a species distinguishes from from MMTV-alpha. These results suggest that the MMTV-beta DNA sequences either are the evolutionary progenitors of the infectious MMTV genome or represent an accumulation of evolutionarily divergent MMTV-alpha insertions into the mouse germ line. (Author abstract) (35 Refs)

49. REGULATION OF THE EXPRESSION OF MOUSE MAMMARY TUMOR VIRUS (MMTV) GP52 EPITOPES (MEETING ABSTRACT).

Tax A, Manson LA
The Wistar Institute, Philadelphia, PA, 19104
Proc Am Assoc Cancer Res; 23:1096 1982

We have applied the lymphocyte hybridoma technology to analysis of the tumor specific antigens displayed on a progressively growing tumor, Mm5mt/c1, which secretes mouse mammary tumor virus (MMTV). To date, all the cloned lymphocyte hybridomas that have been obtained from tumor-bearing animals (rats and C3H/f/C57BL/6 mice) secreting monoclonal antibodies (MCA) directed specifically against this tumor, react with the gp52 of MMTV, the major coat antigen of MMTV. Seven secrete an IgG antibody, whereas four secrete an IgM antibody. Two of the three rat MCA's react with antigenic determinants on the gp52 molecule that are sensitive to NP40. The epitopes with which the other nine MCA's react are stable to NP40. Specificity tests have shown that one MCA is relatively specific for C3H-MMTV and reacts poorly with RIII-MMTV suggesting it may be strain-specific. Three have been found to cross-react completely with both strains of MMTV and are therefore group-specific. Several examples of studies of the expression of the gp52 epitopes using these MCA's as analytical tools, in normal mice, and in tumor-bearing animals as well as studies with species other than the mouse will be shown. (no Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

50. LIPID-PROTEIN METABOLISM IN PATIENTS WITH BREAST CANCER.

Sidorenko LN, Popova SP, Ivanova KP, Korovin KF, Nemirova PE, Selivestrova OS
State Inst. Advanced Training for Physicians, Leningrad, USSR
Vopr Onkol; 28(4):79-81 1982

Relationship between metabolisms of protein and lipid was studied in 64 women (29-60 yr old) with breast cancer (BC). Analysis of serum protein spectrum showed a decrease in albumin fractions and an increase in globulin fractions. The marked dysproteinemia was indicative of impairment of liver function in BC. An increase in serum triglycerides indicated enhanced lipolysis. (12 Refs) (In RUS)

51. AROMATASE IN THE CENTRAL NERVOUS SYSTEM.

Naftolin F, MacLusky NJ
Dept. Obstetrics and Gynecology, Yale Univ. Sch. Medicine, New Haven, CT, 06510
Cancer Res; 42(8,Suppl):3274s-3276s 1982

Central (central nervous system and pituitary) aromatization appears to be a fundamental process for endocrine control and development. Metabolism of androgens to estrogens and the subsequent metabolism of estrogens have been proven in many species, including humans, and linked to estrogen action. Thus, aromatization appears to initiate or to be involved in activities of importance to endocrine function at the central level and their effects peripherally. In the context of breast cancer, central aromatization relates to the control of gonadotrophins and other pituitary-brain hormones which may effect metabolism at the level of the breast. For example, follicle-stimulating hormone can increase aromatization and may be a factor in the control of such metabolism in breast tissue. (Author abstract) (27 Refs)

52. ACTIVATION OF N-OH-AAF BY RAT MAMMARY GLAND PARENCHYMAL CELLS VIA A LIPOXYGENASE-PEROXIDASE ROUTE (MEETING ABSTRACT).

Wong PK, Floyd RA
Oklahoma Medical Research Foundation, Oklahoma City, OK, 73104
Proc Am Assoc Cancer Res; 23:323 1982

The proximate carcinogen, N-hydroxy-2-acetylamino-fluorene (N-OH-AAF) was found to be metabolized into 2-nitrosofluorene (NOF) and N-acetoxy-2-acetylaminofluorene (N-OAc-AAF) by rat mammary parenchymal cells through a peroxidative mechanism. The detection of N-OAc-AAF and NOF as end products by high pressure liquid chromatography (HPLC), the presence of nitroxyl free radical as indicated by electron spin resonance spectroscopy (ESR) and the inhibitory actions of peroxidase inhibitors such as ascorbate and p-aminophenol strongly suggest that peroxidative oxidation is the major route operating in such a system and that neither the acyltransferase nor deacylase route occurs to any appreciable extent. Ram seminal vesicle microsomes also activate N-OH-AAF to NOF. Unlike the prostaglandin synthetase, mammary cell enzymes are not affected by indomethacin or aspirin while lipoxygenase inhibitors, 5,8,11,14-eicosatetraynoic acid (ETYA), gossypol and Fe(III) chelators such as deferoxamine inhibit the cell activity. Externally added arachidonate enhances N-OH-AAF activation. The hydroperoxides generated from exogenous and endogenous arachidonate by the lipoxygenase pathway is believed to be the substrate for the peroxidase activation mechanism. Mammary cells isolated from animals on selenium-supplemented diet are less active than cells from animals on selenium-deficient diet. As selenium was known to inhibit tumor formation on experimental animals, lipoxygenase and peroxidase activities of mammary gland cells appear to be related to mammary carcinogenesis. (no Refs)

53. BIOCHEMISTRY OF AROMATASE: SIGNIFICANCE TO FEMALE REPRODUCTIVE PHYSIOLOGY.

Ryan KJ
Lab. Human Reproduction and Reproductive Biology, Harvard Medical Sch., Boston, MA, 02115
Cancer Res; 42(8,Suppl):3342s-3344s 1982

The formation of estrogens in mammals via aromatase involves the relatively unique capacity to form an aromatic ring de novo in contrast to most other aromatic substances (essential amino acids) which are obtained only in the diet. The reaction is the only example of a cytochrome P-450 system which resides in both the mitochondrial and microsomal fractions of the cell. It occurs widely throughout the body in diverse tissues and functions via both de novo synthesis and transformation of prehormones (androstenedione and testosterone). It is found widely in animal species in both the brain and gonads even in phylogenetically primitive species. Placental aromatase appears to be associated with the evolution of viviparity and an extended gestational period in utero. Follicular aromatase which is dependent upon follicle-stimulating hormone stimulation appears to be essential for oogenesis, ovulation, and normal luteal functions while central nervous system aromatase serves to determine sexual behavior and the neurohormonal link to the hypothalamus and pituitary for ovarian cyclicity. While estrogens are the key to pituitary, breast, and endometrial growth and development, this hormone is one of the few examples of an endogenous steroid that has been implicated as a carcinogen or a stimulant for carcinogenesis. (Author abstract) (18 Refs)

54. GAMMA-GLUTAMYL-TRANSPEPTIDASE ACTIVITY LEVELS IN NORMAL AND TUMOR TISSUES FROM HUMAN MAMMARY GLAND.

Puente J, Varas MA, Barrera I, Sapag-Hager M
Dept. Biochemistry, Faculty Basic and Pharmaceutical Sciences, Univ. Chile, P. O. Box 233, Santiago, Chile
IRCS Med Sci [Cancer]; 9(8):735 1981

Levels of gamma-glutamyl-transpeptidase (GGT) activity in human mammary and tumor tissues (adenocarcinoma and fibroadenoma) were determined. A significant increase in enzyme activity was found in mammary gland adenocarcinoma and fibroadenoma with respect to normal control tissue, suggesting that GGT activity is related to cellular proliferation. The difference in activity of GGT related with amino acid transport may be associated with the tumor state and its maintenance. (5 Refs)

55. STUDIES ON THE DETECTION AND CHARACTERIZATION OF INAPPARENT TRANSFORMED CELLS INDUCED BY NITROSOMETHYLUREA (NMU) IN MAMMARY GLANDS OF NEONATAL BALB/C MICE.

Lum KL
University of California, Berkeley, CA
Diss Abstr Int [B]; 42(12,pt1):4750-B 1982

Neonatal BALB/c female mice were treated beginning at one day of age with 100 ug or 300 ug NMU. Some mice from each of the NMU dosage groups were simultaneously given daily subcutaneous injections of 100 ug deoxycorticosterone (DCA), 0.2 ug estradiol-17beta, 250 ug ovine prolactin (NIH-PS-11) whereas the rest were given only vehicle. All animals were sacrificed at 6-8 days of age and their number 2 mammary glands transplanted as pieces into the gland-free fat pads of 3 week isogeneic virgin mice. Randomly selected glands from all transplant groups were wholemounted after 17 weeks of growth and shown to contain only normal outgrowths. The remaining outgrowths were enzymatically dissociated into single cell suspensions which were then injected into the gland-free fat pads of 3 week BALB/c assay hosts at 10(5) cells per fat pad. These injected cell suspensions gave rise to both normal outgrowths and a variety of morphologically distinct abnormal outgrowths. The incidence of these abnormal outgrowths in the assay glands was dependent upon the dose of NMU used to treat the original neonatal donor mice and on the presence or absence of simultaneous mammotropic hormone treatment. Outgrowths derived from mice given 100 ug NMU without hormone treatment produced an 8% incidence of abnormal outgrowths in the assay glands. Those from mice treated with 100 ug NMU with hormone treatment had a 14% incidence whereas the group treated with 300 ug NMU without hormones had an incidence of 44%. Finally, the group treated with 300 ug NMU and hormones had an incidence of 92%. (no Refs)

56. INDUCTION OF NORMAL AND METAPLASTIC SQUAMOUS DIFFERENTIATION IN DIVERSE ORGANS BY CYCLIC ADENINE NUCLEOTIDE AND PROSTAGLANDINS: HUMAN BREAST (MEETING ABSTRACT).

Schaefer FV, Custer RP, Sorof S
Institute for Cancer Research, Philadelphia, PA, 19111
Proc Am Assoc Cancer Res; 23:139 1982

Squamous metaplasia is a common abnormality of epithelial cell development and differentiation in many organs of animals and humans. We have found that the combination of dibutyryl cyclic AMP, prostaglandins E1, E2, B1, and papaverine (phosphodiesterase inhibitor) in various culture systems not only accelerates normal epidermization in chick embryo skin but also induces squamous metaplasia and keratinization in mouse mammary glands, mouse prostate glands, and breast tissue of women. Dibutyryl cyclic AMP alone at ten-fold higher concentration is highly effective in mouse prostate glands and human breast tissue. The degree of metaplasia and keratinization induced in the cultured breast tissue of premenopausal women depends on the stage of the menstrual cycle at the time of biopsy. Breast tissue of women in the first 10 days of the cycle responds minimally, while that obtained during the final 10 days, when blood levels of progesterone and estrogen are known to peak, produce extensive squamous metaplasia and keratin plaques. Breast tissue of post-menopausal women yield intermediate levels of induction. Retinylidene dimedone or phorbol didecanoate inhibit the induction process. Our findings with the four organ culture systems suggest that cyclic adenine nucleotide, aided by prostaglandins, may act generally as physiological inducers of normal and metaplastic squamous cell development and differentiation in the epithelia of diverse organs. (1 Ref)

57. COMPARISON OF PHASE CONTRAST IMAGES WITH STAINED PREPARATIONS OF HUMAN BREAST CANCER CELLS GROWING IN VITRO (MEETING ABSTRACT).

Volk M, Scheufele J, Rossbach G, Bastert G, Naujoks H
Abteilung fur Klinische Zytologie der Universitatsfrauenklinik, 6000 Frankfurt, W. Germany
Deutscher Kongress fur Zytologie, June 15-16, 1981, Karlsruhe, W. Germany. Deutsher Kongress fur Zytologie, 55 pp., 1981.

Phase contrast microscopy is an important tool for observing unstained cells growing in vitro. However, its use entails specific methodologic problems. Thus features of the specimen are made visible as structural phenomena in the phase image for which we have no empirical yardstick from direct observation at this point. Consequently, specific structures or cell organelles cannot be readily identified just on the basis of certain shade values on the brightness scale. Additional criteria are needed. We cultured human breast cancer cells, directly and following transplantation to nu/nu mice, in vitro in glass and plastic vessels. Images of the cells were subsequently compared in positive phase contrast to preparations of the same cells after May-Grunwald-Giemsa staining, without being subjected to any influence whatsoever (other than dessication and fixation) between the two observations which might have led to changes in cell form. In particular, the monolayer was not detached from the base of the culture vessel. Thus it was possible to check the interpretation of the phase image against the stained preparation. We are of the opinion that this technic will facilitate evaluation of phase contrast images. (no Refs) (In GER)

58. MICROSOMAL METABOLISM OF THE CARCINOGEN, N-2-FLUORENYLACETAMIDE (2-FAA), IN THE RAT MAMMARY GLAND (MEETING ABSTRACT).

Ryzewski CN, Malejka-Giganti D, Polovina M
Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, 55455
Proc Am Assoc Cancer Res; 23:308 1982

Studies of metabolism of 2-FAA in its extrahepatic target were made possible with our new high performance liquid chromatographic method which overcomes previous difficulties in quantitative elution of N-hydroxy-2-FAA and concomitant separation of 8 other metabolites of 2-FAA. Peak detection is by UV absorbance and quantitation is by peak area determination relative to standard curves. We have determined the products which form during incubation of 2-FAA with mammary gland microsomes (MGM) of lactating rats treated with corn oil (control) and 3-methylcholanthrene or beta naphthoflavone. These compounds induced cytochrome P1-450 in MGM and hepatic microsomes (HM). Overall metabolism, indicated by decreases in substrate, was slower in MGM than in HM for equivalent amounts of microsomal protein from rats treated with the inducers. MGM from control rats were capable only of hydroxylation to 9-, 5-and 3-hydroxy-2-FAA. MGM from induced rats had enhanced capacities to hydroxylate to 5-and 3-hydroxy-2-FAA and had the capacities to hydroxylate to 7-hydroxy-2-FAA and most importantly to N-hydroxy-2-FAA, the proximate mammary gland carcinogen. The capacity of MGM of induced rats to convert 2-FAA to N-hydroxy-2-FAA may be of significance in tumorigenesis not only in the mammary gland but in suckling rats as well. (no Refs)

59. EFFECT OF MONOOXYGENASE INDUCERS ON RAT MAMMARY PEROXIDASE AND ARYL HYDROCARBON HYDROXYLASE (AHH) (MEETING ABSTRACT).

Rogan E, Cavalieri E
Eppley Institute for Research in Cancer, Omaha, NE, 68105
Proc Am Assoc Cancer Res; 23:314 1982

Since horseradish peroxidase catalyzes binding of polycyclic aromatic hydrocarbons (PAH) by one-electron oxidation and peroxidase may activate PAH by the same mechanism. We studied the effect of monooxygenase inducers on rat mammary peroxidase, and compared it to induction of AHH. Female, 50-60-day-old Sprague-Dawley rats were treated for 2 days prior to killing with 5,6-benzoflavone (BF) or 3-methylcholanthrene (MC) by injection ip or sc at the second and fifth nipples on each side of the rat. BF and MC were injected ip in olive oil at 80 mg/kg and 40 mg/kg bw, respectively, and both sc at 50 nmole/nipple in 5 ul dimethyl sulfoxide (DMSO). Peroxidase and AHH were assayed with guaiacol and benzo[a]pyrene, respectively, as substrates. Peroxidase was significantly induced by ip injection of BF and possibly of MC, when compared to untreated controls. Olive oil caused a smaller, but significant, increase in peroxidase activity. The effect of BF and MC injected sc was less certain, because of the increased peroxidase activity caused by DMSO. Olive oil ip and DMSO sc significantly reduced AHH. However, BF injected ip overcame the solvent effect and significantly increased AHH, compared to the untreated and solvent groups. MC injected ip, and BF and MC injected sc reversed some of the decrease in AHH caused by olive oil and DMSO. The effects of monooxygenase inducers on peroxidase were greater than those on AHH. (no Refs)

60. HUMAN BREAST CELL MEDIATED MUTAGENESIS (MEETING ABSTRACT).

Gould MN, Cathers LE, Moore CJ
Department of Human Oncology, University of Wisconsin, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:317 1982

We compared the ability of human and rat mammary cells to activate chemical carcinogens. Both human and rat mammary glands were enzymatically dispersed and separated into stromal and parenchymal enriched populations. The natures of these fractions were confirmed by light and electron microscopy. Stromal and parenchymal populations from both species were cultured at varying cell densities. After the mammary cells attached, they were irradiated with 5000 rad and then cultured with V-79 cells. The co-cultures were exposed to DMBA (dimethylbenzanthracene) (1 ug/ml) for 45 hours. The cultures were then washed and the V-79 cells were removed and assayed for the induction of mutations at the HGPRT locus. Each of the four cell populations activated DMBA. The number of induced mutants was related to the density of mammary cells plated within each species. We found that both the parenchymal and stromal cells could activate DMBA to an equivalent extent, as measured by induced mutation. However, at optimal cell densities the rat cells induced about four times the number of mutations as did the human cells. In addition, we compared these cells for the ability to convert polycyclic hydrocarbons to water-soluble metabolites. Both human and rat stromal cells were more efficient at converting DMBA and BP to water-soluble products than were their respective epithelial cell populations. Rat stromal and parenchymal cells converted BP to water-soluble derivatives more efficiently than their human counterparts. (no Refs)

61. RELATIONSHIP OF POLYCYCLIC HYDROCARBON (PH) METABOLISM IN RAT MAMMARY CELLS TO TUMOR SUSCEPTIBILITY IN VIVO (MEETING ABSTRACT).

Moore CJ, Bachuber AJ, Gould MM
Department of Human Oncology, University of Wisconsin, Madison, WI, 53792
Proc Am Assoc Cancer Res; 23:318 1982

Since tumor induction rates by PHs vary widely among rat strains, we have confirmed the high susceptibility of Sprague-Dawley (SD) rats to mammary tumorigenesis by 7,12-dimethylbenz(a)anthracene (DMBA) compared to the Long-Evans (LE) strain. We have also found a similar difference between two inbred rat strains, Wistar-Furth (W/Fu) and F344, respectively. Using cultured mammary cells, divided into epithelial or stromal enriched populations, from these 4 strains, we examined DMBA and benzo(a)pyrene (B(a)P) metabolism in relation to in vivo differences in tumor induction rates. B(a)P was converted to water-soluble metabolites at significantly higher rates than DMBA, with a constant ratio of metabolism of the two PHs, in all cell systems tested. The stromal cell populations, which are less susceptible to carcinogenesis in vivo, converted B(a)P and DMBA to water-soluble metabolites 2-4 times faster than the epithelial cell cultures. In contrast, cells from the high susceptibility strains, SD and W/Fu, showed higher levels of water-soluble metabolite production than the less susceptible strains. High-pressure liquid chromatographic analysis of ethyl acetate-extractable B(a)P metabolites formed in both mammary cell populations from all 4 strains revealed predominantly 9,10-and some 7,8-dihydrodiol formation, but no major differences by cell type or rat strain. We have measured activation of DMBA and B(a)P to mutagenic metabolites by mammary cells from SD and LE rats, and found similar rates in both strains. (no Refs)

62. ESTROPHILIN LEVELS AND RNA POLYMERASE ACTIVITY IN 7,12-DIMETHYLBENZ(A)ANTHRACENE (DMBA)-INDUCED MAMMARY TUMORS IN RATS (MEETING ABSTRACT).

Mohla S, Hunter JB
Howard University Cancer Center, College of Medicine, Washington, DC, 20060
Proc Am Assoc Cancer Res; 23:944 1982

Approx 60% of breast cancer patients have estrophilin (ER) of which two thirds respond favorably to hormonal therapy. Estrogens act on their target tissues by interacting with followed by translocation of the ER complex into the nucleus, resulting in increased RNA synthesis as evidenced by increased RNA polymerase activity. Using DMBA-induced mammary tumors in rats, experiments were designed to see whether RNA polymerase activity of isolated tumor nuclei may be related to their cytoplasmic ER levels. Mammary tumors were induced by a single intragastric feeding of 20 mg DMBA in 2.0 ml peanut oil. Mammary tumors were analyzed for ER using dextran coated charcoal or sucrose density gradient methods and tumor nuclei were analyzed for RNA polymerase (alpha-amanitin resistant) activity as described. A value of greater than 10 fmoles/mg protein was considered ER positive. The results indicate comparatively lower RNA polymerase activities in ER positive compared to ER negative tumor nuclei: (a) 77% (10/13) of ER positive and only 17% (1/6) of ER negative tumors exhibited low RNA polymerase activity (less than 200 pmoles 3H-UMP (uridine monophosphate)/mg DNA), (b) the incorporation of 3H-AMP or 3H-GMP (guanosine monophosphate) into RNA was also lower in ER positive tumors than in ER negative tumors. The results indicate significant correlation between ER levels and RNA synthesis and suggest additional biochemical parameters to distinguish between hormone dependent from independent tumors. The possible clinical implications of these data remain to be elucidated. (no Refs)

63. TUMORS CULTURED ON DIFFERENT SUBSTRATES (MEETING ABSTRACT).

Emerman JT, Siemiatkowski JM, De Jong G
Department of Obstetrics and Gynecology, University of British Columbia, Vancouver, V5Z 1M9, Canada
In Vitro; 18(3,part2):280 1982

When studying the growth of tumor cells in culture, tumor heterogeneity as well as environmental factors must be considered. We compared the growth dynamics and tumorigenicity of cells from androgen-responsive Shionogi mouse mammary tumors cultured on different substrates. Tumors were dissociated in saline-versene-trypsin. Cells were seeded at 10(5) cells/cm2 onto collagen gels or plastic Petri dishes. Cultures were maintained for 10 days in DME (Dulbeccos modified Eagles medium) containing 5% FBS (fetal bovine serum), 0.01 ug/ml dihydrotestosterone and 5 ug/ml insulin. Although the cell number doubled after 10 days on both substrates, the proliferative cell compartment on gels was different from that on plastic. Two subpopulations of cells which varied in cellular DNA content were identified using flow cytometry. The predominant cell type growing on collagen gels was heteroploid, while cells on plastic were mainly diploid. Tumorigenicity was assayed by injecting 10(6) cells subcutaneously into host mice (DS strain). Tumors arising from cells cultured on gels appeared twice as fast as those from cells cultured on plastic. The results show that the ratio of one cell population to another differed markedly on the 2 substrates. (no Refs)

64. RESISTANCE OF TERMINAL DIFFERENTIATION IN PRECANCEROUS MAMMARY HYPERPLASIA (MEETING ABSTRACT).

McGrath CM, Soule HD
Michigan Cancer Foundation, Detroit, MI, 48201
Proc Am Assoc Cancer Res; 23:904 1982

Acquired resistance to terminal differentiation is a crucial step in neoplastic transformation of cells that grow by differentiative renewal (eg mammary cells). We sought to determine if such resistance was already acquired at the precancerous stage of mammary cell transformation, and if it was associated with new responsivity to hormones normally controlling proliferation. Hyperplastic ductal and alveolar foci, induced by DMBA (dimethylbenzanthracene) and oncogenic viruses respectively, were isolated from Balb/c mouse mammary glands. Cells were pseudocloned from individual atypias on collagen-coated substrates and tested for accumulation of casein (a marker for endpoint differentiation) in response to insulin (I), cortisol (F) and prolactin (M). Responsivity of differentiation-resistant and sensitive cells to mitogens was determined by replica plating corresponding colonies. Persistant precancerous hyperplasias, both ductal and alveolar, but not benign involutional hyperplasias, contained reduced numbers of cells responsive to IFM, when compared to normoplastic controls. Results of replica plating experiments in which proliferative responsivity of cells to epidermal growth factor (EGF) was measured autoradiographically, suggest that cells resistant to terminal differentiation are also more responsive to EGF. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

65. BIOCHEMICAL MARKERS FOR CANCER.

Chu TM
Dept. Diagnostic Immunology Res. and Biochemistry, Roswell Park Memorial Inst., Buffalo, NY
Clin Biochem Anal; 11:375 1982

Selected topics on biochemical markers, which have been utilized in clinical oncology, are presented and a possible approach to the study of the basic mechanism of the marker at the molecular level is described. Topics related to biochemical markers are discussed under the following headings: immunological approach to the biochemical markers for cancer, alpha fetoprotein, carcinoembryonic antigen as a tumor marker, enzymes as tumor markers, developmental alkaline phosphatases as biochemical tumor markers, prostatic acid phosphatase in human prostate cancer, biochemical markers for the differential diagnosis of leukemias, steroid-receptor interactions in normal and neoplastic mammary tissues, alteration and clinical significance of alteration of isoferritins in human malignancy, polyamines as biochemical markers of tumor growth parameters, ectopic hormone production by tumors, immunoglobulins as cancer markers in humans, multiple markers in the management of cancer patients, protein markers for androgenic activity in rat ventral prostate. (1283 Refs)

66. ALCOHOL AND CARCINOGENESIS.

Seitz HK, Czygan P, Kommerell B
Schwerpunkt Gastroenterologie, Medizinische Universitatsklinik, Bergheimer Str. 58, D-6900 Heidelberg 1, W. Germany
Leber Magen Darm; 12(3):95-107 1982

The relationship between alcoholism and carcinogenesis is reviewed. Alcohol has been linked to increased incidences of cancers of the oropharynx, larynx, esophagus, liver, and probably the pancreas and rectum. Beverages with high alcohol content present greater risks than wine or beer. Alcoholism has a synergistic effect on carcinogenesis caused by smoking. Cirrhosis of the liver caused by alcoholism is important as a precancerous condition. Beer consumption increases the risk of pancreatic cancer; chronic pancreatitis is not involved as an intermediate stage. Beer consumption also increases the incidence of rectal cancer. Other cancers possibly related to alcohol abuse include carcinomas of the kidney, prostate, bladder, breast, and thyroid. Animal studies indicate that alcohol by itself is not carcinogenic. Alcohol apparently has a cocarcinogenic effect. Alcohol may induce specific enzyme systems that interact with carcinogens. It may be active in either the initiation phase, the promotion phase, or both. In the gastrointestinal tract it may induce carcinogenesis by local effects. Systemic effects include alterations in hormonal and immune functions, as well as in the actions of vitamins and minerals. In addition, alcoholic beverages contain a number of carcinogenic substances. (179 Refs) (In GER)

67. CARCINOGENESIS AND BIOLOGICAL EFFECTS OF TUMOR PROMOTERS.

Hecker E
Inst. Biochemistry, German Cancer Res. Center, Heiodelberg, W. Germany
Carcinogenesis. Vol. 7, 664 pp., 1982.

The most recent experimental findings on the etiological, cell biological, and molecular facets of carcinogenesis are reviewed. The basic problems of whether specific carcinogens function as promoters of carcinogenesis, as stimulators of initiation, or both, are addressed with respect to in vivo animal studies, epidemiological studies, and in vitro studies of tumor promotion. Carcinogenesis and tumor promotion in vivo is discussed with respect to the skin as a target tissue and nonepidermal target tissues. Effects of tumor promoters on cell proliferation and differentiation are reviewed for the epidermis and nonepidermal cell systems. Membrane interactions and receptors, effects on intercellular communication and cell metabolism, and viral and immunologic aspects are reviewed. Epidemiologic studies of esophageal cancer in Linxian County, China, nutritional carcinogenesis, and breast cancer as an example of promoting effects are discussed. (1368 Refs)

68. REVIEW OF STUDIES ON ESTROGEN BIOSYNTHESIS IN THE HUMAN.

Siiteri PK
Dept. Obstetrics, Gynecology, Reproductive Sciences, Reproductive Endocrinology Center, Univ. California, San Francisco, CA, 94143
Cancer Res; 42(8,Suppl):3269s-3273s 1982

While the gonads and placenta are usually thought of as the principal sites of estrogen synthesis, many other tissues are now known to contain the aromatase enzyme. Despite a wealth of information, the functional significance, if any, of this widespread distribution is not yet clear. Nonetheless, elevated estrogen production resulting from either an apparent increase in enzyme activity or increased substrate availability in blood can have important effects on target tissues such as the breast, uterus, and bone. Our early studies suggesting that aromatase inhibitors can effectively reduce the impact of peripheral estrogen synthesis have been amply confirmed by the elegant studies of Santen and others. Many previous studies have suggested that aromatase activity may be present in breast tumors. The profound implications for growth of estrogen-sensitive tumors led us to reevaluate this question. Using a sensitive modification of our original radiometric aromatase assay, we have found detectable activity in only about 40% of human breast tumors (n = 100). Only rarely (1/100) does the aromatase activity exceed 1.0 pm/hr/g tissue or 0.001% of that found in the human placenta. These quantitative results contradict several published reports which suggest that most breast tumors contain biologically significant levels of aromatase activity. (Author abstract) (54 Refs)

69. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.

Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
Isr J Med Sci; 18(4):433-438 1982

The possible association of oral contraceptives (OC) and menopausal estrogens (ME) on development of breast cancer is reviewed. The high incidence of breast cancer concurrent with extensive OC-ME usage, considered together with the relatively high hormone dependence of breast tumors and the placement of the breast as a target organ in the estrogen-progesterone hormonal pathways supports this association. Theories of the hormonal etiology involve estriol, progesterone, androgens, and the pineal gland; however, the specific hormonal etiology is unclear. Most studies have demonstrated significantly decreased risk of benign breast disease in women using OC. Since increased parity and early first birth are potentially protective conditions for breast cancer, OC, by simulating pregnancy, may exert a protective effect. The incidence of benign breast disease appears to be inversely related to the amount of progesterone in different OC. No significant overall increase in the risk of breast cancer has been demonstrated among users of OC. However, specific subgroups in which an increased risk was shown have been identified, including women with previous biopsy of benign breast disease. Evidence is available associating ME with an increased risk of endometrial carcinoma. Recent studies have demonstrated a positive association between ME and breast cancer. Caution is suggested in long-term use of OC and the continuous use of ME for periods greater than 10 yr should be reconsidered. (57 Refs)

70. RADIATION AND HUMAN HEALTH.

Gofman JW
Univ. California, Berkeley, CA
Radiation and Human Health. San Francisco, Sierra Club Books, 908 pp., 1981.

The relationship between radiation and human health is considered under the following chapter headings: energy interchanges and health, origins of human cancer, induction of cancer and leukemia by ionizing radiation, a systematic approach to the quantitative aspects of radiation carcinogenesis, with personal and public health risk estimates, human epidemiological evidence concerning radiation carcinogenesis, induction of human breast cancer by ionizing radiation, from peak percents to whole-body cancer doses by age at irradiation, practical applications of the whole-body cancer dose, partial-body irradiation and cancer doses for specific kinds of cancers, evidence for a linear or supralinear dose-effect relationship and for the nonexistence of a 'threshold' dose, handling the internal emitter; internal alpha emitter, biologically important, man-made alpha-particle-emitting nuclides (plutonium and other transuranics), lung cancers already produced by plutonium inhalation, plutonium-induced lung cancers in a plutonium energy economy, likely radiation doses and their effects in a nuclear-power economy, ionizing-radiation exposures from natural sources, consumer products, and particular occupations, ionizing-radiation exposures from medical diagnostic and therapeutic irradiation, induction of human leukemia by ionizing radiation, congenital effects of ionizing radiation, and genetic and chromosomal effects of ionizing radiation. (299 Refs)

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NOTICE OF CURRENT REVIEWS: CARCINOGENESIS

As an additional service to readers of carcinogenesis (CK series) CANCERGRAMS, each issue now provides a bibliography of review articles of interest to carcinogenesis researchers, selected from journals screened for that month's CANCERGRAMS.

CHEMICAL CARCINOGENESIS

1. ASBESTOS CARCINOGENESIS: ASBESTOS INTERACTIONS AND EPITHELIAL LESIONS IN CULTURED HUMAN TRACHEOBRONCHIAL TISSUES AND CELLS.
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2. REVIEW: ORAL CONTRACEPTIVES AND MENOPAUSAL ESTROGENS IN RELATION TO BREAST NEOPLASIA.
Brzezinski A, Schenker JG
Dept. Obstetrics and Gynecology, Hadassah Univ. Hosp., POB 12000, 91120 Jerusalem, Israel
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3. LIVER DISEASES DUE TO HORMONAL CONTRACEPTIVES.
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RADIATION CARCINOGENESIS

4. THE WORK OF THE NRPB 1977/80 AND A REVIEW OF THE FIRST 10 YEARS.
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DIETARY FACTORS IN CARCINOGENESIS

5. ALCOHOL AND CARCINOGENESIS.
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6. ZINC, COPPER, AND MANGANESE IN IMMUNE FUNCTION AND EXPERIMENTAL ONCOGENESIS.
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9. NASAL CARCINOMA IN WOODWORKERS: A REVIEW.
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12. INHALATION CARCINOGENESIS: AN OVERVIEW.
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18. CARCINOGENESIS AND BIOLOGICAL EFFECTS OF TUMOR PROMOTERS.
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VIRAL AND IMMUNOLOGICAL ASPECTS OF CARCINOGENESIS

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Larsen KH, Brash D, Cleaver JE, Hart RW, Maher VM, Painter RB, Sega GA
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EPIDEMIOLOGY OF BREAST CANCER IN HUMAN POPULATIONS

1. TREND IN TUMOR INCIDENCE AND POSSIBLE RELATION TO CANCER SCREENING.

Neumann G
Hohe Strasse 28, D-7000 Stuttgart 1, W. Germany
Fortschr Med; 100(23):1073-1078 1982

Trends in incidences of various malignant tumors and their relation to participation in screening programs are discussed with emphasis on the current situation in the Federal Republic of Germany. In general, absolute numbers of cancer cases are increasing as the result of changes in the age-distribution of the general population. The incidence of lung cancer is increasing, while that of gastric cancer is decreasing. In industrial nations the mortality due to intestinal, rectal, and prostatic cancers

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among men is rising. Among women, the incidences of uterine and gastric cancers are decreasing, while those of lung and breast cancers are increasing; trends in incidences of rectal and intestinal cancers are not uniform. Participation in screening programs generally correlates inversely with mortality. Participation is highest among age groups with low incidences of cancer; screening therefore has limited effect on the epidemiology of cancer. In one period the mortality due to colon, rectum, breast, or prostate was higher than expected in spite of cancer screening. In contrast, cervical cancer mortality was lower than would be expected from screening. Because the site of many uterine cancers is not recorded, mortality rates for cervical cancer are not very useful. (20 Refs) (In GER)

2. TRENDS IN CANCER EPIDEMIOLOGY (MEETING ABSTRACT).

Miller AB
NCIC Epidemiology Unit, University of Toronto, Toronto, Ontario, Canada
American Cancer Society National Conference: The Primary Care Physician and Cancer, June 24-26, 1982, Washington, DC American Cancer Society; :A3 1982

The increase in lung cancer in men has come to an end at younger ages and is slowing at older ages. However, in women the increase continues and by the end of this decade lung cancer may be the most important cause of cancer deaths in women. The incidence of prostate and breast cancer continues to increase but mortality is stable, suggesting changes in diagnostic practices. Mortality from stomach cancer and from cancer of the cervix in women continues to fall. Increasingly it is necessary to recognize the multifactorial causes of cancer, requiring detailed information on lifestyle, occupational and sometimes residential histories to unravel etiology. Physicians need to understand the requirements for access to patients in order to obtain data for studies. Monitoring for unexpected hazards will require record linkage, particularly using the National Death Index. Such sources can be used with preservation of confidentiality while increasing knowledge for primary prevention. (no Refs)

3. THE INCIDENCE OF BREAST CANCER: ANALYSIS OF THE AGE DEPENDENCE.

Dix D, Cohen P
Dept. Biology and Health Science, Univ. Hartford, West Hartford, CT, 06117
Anticancer Res; 2(1/2):23-27 1982

Female breast cancer (FBC) incidence was studied as a function of age in 71 different populations throughout the world. Incidence data was normalized for differences in frequency of occurrence. Mean percentage incidence of FBC among all populations studied showed an exponential increase from age 20 to 45 yr; a decrease after age 45 yr suggests an influence of menopause. Populations were not randomly distributed about the total population median normalized incidence at various ages. The populations were then classified according to their age-incidence patterns in three groups with median incidence after age 69 yr of 50%, 47%, and 31% in Group 1, 2, and 3, respectively. At most age intervals, the normalized incidence in the 24 Group 1 populations was less than the total medium, while the normalized incidence in the 26 Group 3 populations was greater than the total median. While the possibility cannot be excluded that the variation in age-incidence patterns among the population groups is an artifact of tumor registration errors, evidence suggests that such an artifact is unlikely. FBC occurs more frequently in Group 1 populations than in Group 3 populations. It is suggested that Group 3 populations may share an element of protection from, or that Group 1 populations may share an element of risk for, breast cancer. (12 Refs)

4. RECENT TRENDS IN CANCER INCIDENCE IN KIEV 1969-1979.

Guslitser LN, Matvilchuk YD
R. Kavetsky Inst. for Oncology Problems, 252 127 Kiev, USSR
Neoplasma; 29(2):129-134 1982

The analysis of the trends of age-adjusted incidence rates of malignant tumors in the city of Kiev in the yr 1969-79 revealed a gradual increase of the majority of individual sites, mainly of the malignant tumors of rectum, lymphoid and hematopoietic tissues in both sexes and of breast in females. On the other hand a decrease of incidence rates of the malignancies of skin, lip and stomach in both sexes and of esophagus, lung and uterine cervix in females was noted. These investigations formed the basis of the prognosis study of incidence rates of malignant tumors in Kiev until 1990. The importance of the study of incidence rates and trends of individual sites of malignant tumors for the investigation of their factors and causes in urban conditions and environment is emphasized. (Author abstract) (8 Refs)

FACTORS THAT INFLUENCE THE RISK OF BREAST CANCER

5. EPIDEMIOLOGY OF BREAST CANCER.

Marchant DJ
Tufts-New England Medical Center, Boston, MA
Clin Obstet Gynecol; 25(2):387-392 1982

The incidence of breast cancer (BC) and risks associated with BC are discussed. A number of factors have been associated with increased risk for BC including demographic, anthropometric, dietary, menstrual, reproductive, hormonal, genetic, and others, including a history of benign breast disease. Key risk factors include previous cancer of one breast, age, age at menarche, age at full-term pregnancy, age at menopause, and wt. The woman with previous cancer of one breast is at risk for cancer in the opposite breast. Studies indicate that the risk is approx 1% per yr. Evidence suggesting that estrogens play an important part in determining the hormonal milieu that favors the development of human BC exists. Risk factors noted in epidemiologic studies are associated with changes in the production of estrogen. Height and wt factors that contribute to increased risk in postmenopausal women can be explained by increased peripheral conversion of androgen to estrogen. The administration of estrogens to postmenopausal women may result in a small increase in the risk of BC. Growth rate of human malignant BC cells in tissue culture is enhanced by estrogens in physiologic concentration. Therapeutic strategies that are effective in the treatment of BC in premenopausal women can be explained on the basis of reduction or elimination of endogenous estrogens. Recent studies on the mechanism of action of estriol indicate that it is neither an impeded estrogen nor an estrogen antagonist when present in continuous of chronic fashion. Most investigators suggest that estrogen is preparative rather than carcinogenic. One of the risk factors that is alterable is obesity, particularly in the postmenopausal woman. (14 Refs)

6. MALIGNANCIES AND EXPOSURE OF THE YOUNG TO IONIZING RADIATION.

Schull WJ, Kato H

Center for Demographic and Population Genetics, Univ. Texas Health Science Center at Houston, Houston, TX

Cancer Bull; 34(3):84-89 1982

Risk of radiation-related malignancies in individuals exposed in the first two decades of life in Hiroshima and Nagasaki is described. The relative risk of death due to leukemia in the 'heavily' exposed, particularly among those individuals exposed in the first decade of life, is much higher than the relative risk for exposures at subsequent ages. For the three most common radiation-related malignancies, cancers of breast, lung, and stomach, the absolute risk of death, for age-at-death specific groups, is higher the younger the age at the time of the bombing (ATB). Carcinoma of the thyroid was diagnosed during life more commonly in persons who were less than 20 yr of age ATB. The excess incidence of the malignancy/10(6) person-yr-risk/rad was 2.1, 2.3, 0.33, 0.28, and-0.07 for exposures at less than 10, 10-19, 20-34, 35-49, and 50 or more yr of age ATB, respectively. A study of 339 fatal and nonfatal malignancies among young survivors in the period 1950-1974 demonstrated that aside from the increased frequency, the distribution of malignant solid tumors differed little from that seen among individuals who were 20 yr of age or older when exposed. The diminished risk of radiation-related breast cancer among females exposed in the circum-menopausal years suggests that the endocrinologic status and possibly other factors may influence this specific risk. Whether the increased risk extends uniformly to all exposed individuals or whether there are especially vulnerable, 'high-risk' persons, is unknown. (26 Refs)

7. BREAST CANCER AND SERUM CHOLESTEROL.

Hiatt RA, Friedman GD, Bawol RD, Ury HK

Dept. Medical Methods Res., Kaiser-Permanente Medical Care Program, 3451 Piedmont Ave., Oakland, CA, 94611

JNCI; 68(6):885-889 1982

Recent studies have suggested a role for dietary fat in the etiology of breast cancer. The relation of serum cholesterol and other serum lipid measures to breast cancer incidence was investigated in a cohort of 95,179 women who had multiphasic health checkups from 1964 through 1972. Through 1977, 1,035 new breast cancer cases occurred in over 752,000 person-yr of follow-up. Age-adjusted incidence rates were 1.45, 1.37, 1.31, and 1.40/1,000 person-yr from the lowest to the highest quartile of serum cholesterol level, respectively. Similarly, no statistically significant relation was detected between beta-lipoprotein of total lipids and breast cancer. The sample size was sufficiently large to have detected a relative risk of 1.4 or larger with a probability of 99.9% at the 0.05 level of significance. The expected relation of breast cancer to established risk factors was confirmed by univariate analysis, and serum cholesterol and breast cancer were not associated after simultaneous consideration of nine other risk factors by multivariate analysis. These data suggest that the postulated causal relation between dietary fat and breast cancer does not act via an effect on circulating lipid levels. (Author abstract) (37 Refs)

8. MAMMOGRAPHIC PATTERN AND BREAST CANCER RISK FACTORS IN POST-MENOPAUSAL WOMAN (MEETING ABSTRACT).

Walsh PV, Whitehouse GW, Evans A, George WD

Department of Surgery and Radiodiagnosis, Royal Liverpool Hospital, Liverpool, England

Clin Oncol; 8(1):85 1982

The mammographic findings of dysplasia (DY) and prominent ducts (P2) have been described as risk factors for breast cancer (Wolfe, 1976). The aim of this study was to define the relationship between mammographic pattern and classical risk factors (age at menarche and menopause, parity and past or family history of breast disease). The analysis was carried out on 892 normal women who attended a breast screening unit and who were more than 5 years post-menopausal. Early menarche (before age 14) normally considered a high risk factor was found to correlate strongly with low risk mammographic patterns. Age at menopause, and a family history of breast cancer, also considered to be indicators of risk, did not correlate with any particular x-ray pattern. Conversely nulliparity, an indicator of high risk, correlated significantly with high risk mammograms as did a past history of benign biopsy. For parous women, the age at first birth correlated with x-ray pattern. Women first parous before the age of 25 had a significantly higher incidence of low risk patterns when compared with women first parous after 25. (1 Ref)

9. A POPULATION-BASED STUDY OF FAMILIAL ASPECTS IN SOFT TISSUE SARCOMAS OF CHILDHOOD (MEETING ABSTRACT).

Birch JM, Hartley AL

University of Manchester, Manchester, England

Twenty-third Annual General Meeting of the British Association for Cancer Research, March 29-31, 1982, Edinburgh, Scotland. British Association for Cancer Research 78 pp., 1982.

A familial syndrome involving soft tissue sarcomas (STS) in children and early onset breast cancer in their mothers has been described. At present neither the proportion of familial childhood STS nor the risk to the mothers can be estimated. The present study, based on the Manchester Children's Tumor Registry (MCTR), seeks to do this and to identify features which distinguish familial from non-familial cases. Between 1954 and 1981, 154 cases of STS were included in the MCTR. The ratio of boys to girls was 1.4:1. The median age at onset was 4 years among the largest group, the rhabdomyosarcomas. A search of the MCTR records of these 154 cases revealed: (a) 5 sib-pairs involving a STS compared with 5 sib-pairs with other tumors, among approximately 2,800 cases in the MCTR as a whole; (b) two mothers with early onset breast cancer, including the mother of one of the sib-pairs; and (c) 14 other cases with close relatives who had early onset breast, childhood or other cancers. In addition 9 of the 154 cases had congential abnormalities and 5 had 1 or more 1st degree relatives with congenital abnormalities. There were four cases who were one of a pair of twins and 5 cases who had twins among their close relatives. This response an increased frequency of both congenital malformations and twinning. (no Refs)

10. PEUTZ-JEGHERS SYNDROME AND BILATERAL BREAST CARCINOMA.

Trau H, Schewach-Millet M, Fisher BK, Tsur H
Dept. Dermatology, Chaim Sheba Medical Center, Tel-Hashomer, Israel
Cancer; 50(4):788-792 1982

Bilateral breast carcinoma developed in a young woman with Peutz-Jeghers syndrome. A review of the literature reveals that it is not uncommon for Peutz-Jeghers syndrome to be associated with malignant tumors. A genetic predisposition to cancer development may be part of the spectrum of this syndrome. Patients with Peutz-Jeghers syndrome should be examined carefully for early detection of cancer. (Author abstract) (50 Refs)

POSSIBLE IATROGENIC FACTORS IN HUMAN BREAST CARCINOGENESIS

11. HORMONES AND MEDICATIONS (MEETING ABSTRACT).

Lipsett MB
National Institutes of Health, Bethesda, MD, 20205
American Cancer Society National Conference: The Primary Care Physician and Cancer, June 24-26, 1982, Washington, DC American Cancer Society; :A7 1982

Hormones have been shown experimentally to act as cocarcinogens or promoters, ie, they facilitate the carcinogenic event. In the cases of breast and endometrium, those hormones that facilitate growth may also favor carcinogenesis in the human. There is good epidemiologic evidence of breast and endometrial cancer, the risk increasing with increasing duration of use. Periodic progestin-induced withdrawal will probably mitigate the risk of endometrial cancer after the menopause. Prolactin is the important promoter of mammary cancer in the rat and mouse, but its significance in women is still under study. Intermittently elevated prolactin levels have been noted in some women who subsequently developed breast cancer, but epidemologic studies of women who have received prolactin-releasing drugs such as reserpine and perphenazine have not disclosed increased risk. Diethylstilbestrol is listed as a carcinogen but any estrogen can induce mammary cancer in the rodent or vaginal adenosis in the neonatal mouse (an experimental model of human vaginal adenocarcinoma). (no Refs)

12. IONIZING RADIATIONS: DNA DAMAGE, MUTAGENICITY AND MORPHOLOGICAL TRANSFORMATION IN MAMMALIAN CELLS. CARCINOGENICITY IN RODENTS AND IN HUMAN.

Parodi S, Taningher M, Toma S, Scarpati D, Santi L
Dept. Oncology, Genoa Univ., Genoa, Italy
Acta Thermogr; 6(1-3):10-15 1981

The relationship between ionizing radiations, modification of DNA, mutagenicity and carcinogenicity is reviewed. The energies associated with ionizing radiations range from 10(2)-10(4) electron volts for diagnostic x-rays to 10(9) electron volts for the highest radiations used in radio-therapy. In female breasts, 100-300 rad doses gave an approximate increase of cancer of 2% compared to a control group, with an av latency of 24 yr. Biological models favor a nonlinear relationship between dosage and effect, especially when comparing very small and av cumulative dosages. It is possible to reach, during the lifetime of an individual, cumulative doses of about 200 rads or more; therefore the cumulative radiation exposure during the lifespan of each patient should be recorded. Radiological examinations in young asymptomatic women should be viewed with caution, in terms of risk-benefit assessment, considering the essential role played by latency time in tumor development. (27 Refs)

13. ESTROGEN REPLACEMENT: ITS BENEFITS AND ITS RISKS.

Skillman TG
Ohio State Univ. Coll. Medicine, Columbus, OH
Consultant; 22(7):115,116,119,125,127 1982

Benefits and risks of estrogen replacement therapy (ERT) are evaluated. ERT counteracts the effects of estrogen depletion. Specific indications for ERT include vasomotor hyperactivity, depression, gynecologic problems, and osteoporosis. Risks of ERT include a higher rate of endometrial cancer, unmasking of hypertension, generation of lithogenic bile, modification of lipoproteins, and disturbances of the clotting mechanism. ERT apparently does not increase the risk of breast cancer. A determination for or against use of ERT depends on evaluation of factors in each case. (7 Refs)

14. ORAL CONTRACEPTIVE STEROIDS AND MALIGNANCY.

Grant E
No affiliation given
Clin Oncol; 8(2):97-102 1982

Current literature data on the cancer incidence among the users of oral contraceptive steroids (OCS) are reviewed. The use of OCS was shown to be associated with considerable increase of the incidence of breast cancer and cervical cancer. The largest increase in the incidence of breast and cervical cancer was observed in women 15-24 yr old who have a risk of double exposure to exogenous hormones. (29 Refs)

15. BREAST EXAMINATION IN MEDICAL PRACTICE.

Kucera H, Kubista E
Dept. Obstetrics and Gynecology, Univ. Hosp., Vienna, Austria
Acta Thermogr; 6(1-3):46-50 1981

The usefulness of mammography (MG) combined with contact thermography (CT) in the detection of breast lesions is discussed. MG is very accurate, but has a limited role in screening for breast cancer because of its high cost and radiation risk following repeated investigations, particularly in younger women. In previously reported series, about 80% of breast cancers were identified in women older than 50. Clinically diagnosed breast cancers were more than 3 cm in diameter in over 50% of cases. Periodic clinical check-up could reduce the av size of breast tumors below that which are detected by women themselves. The use of CT as a complementary procedure to physical examination of the breast is justified by its non-invasive nature, its simplicity, and its low cost. The false negative rate of CT (10%) and MG (9.3%) can be reduced to 1.3% when the two procedures are used in combination. In non-symptomatic women under 35 yr old, MG can be avoided if physical and CT examinations are negative MG is recommended for the patient between 35-50 yr old, however, should be repeated every 3-5 yr. Any clinical pathological findings in symptomatic women must be followed by MG and eventually by CT. (4 Refs)

16. EPIDEMIOLOGICAL ISSUES IN BREAST CANCER SCREENING.

Bruzzi P, Puntoni R, Toma S
Scientific Inst. Study and Treatment of Cancer, Genoa, Italy
Acta Thermogr; 6(1-3):50-56 1981

Breast cancer risk factors include age, familiarity, nulliparity, late first pregnancy, early menarche, late menopause, chronic breast disease, obesity, hyperlipidic diet, associated diseases, and intake of exogenous estrogens. In evaluating costs, side-effects and benefits of a screening program for breast cancer, problems associated with efficacy, prevalence rate and case-fatality ratio of the disease, and accuracy, costs and side-effects of diagnostic tests must be considered. Physical examination of the breast is very inexpensive, does not require any device or particular technical skill, and does not involve any risk for the screened patient. However, it is estimated to have a sensitivity/specificity of 80%/70%. Mammography (MG) shows much higher sensitivity/specificity (90%/99%) and is capable of detecting cancers at an earlier stage. However, it is costly, requires radiographic facilities, the presence of trained personnel, and has an associated risk of radiation exposure. Thermography (TG) has a sensitivity/specificity of 80%/90%, is low cost, involves no risk, however, is time-consuming, and requires the presence of trained personnel. A possible approach to large scale breast screening could be a sequential screening program in which all women of certain age groups undergo both physical examination and TG, while MG is carried out only on women positive in either test. This approach would select for MG about one-third of the female population in which about 96% of all breast cancer cases are present. (11 Refs)

INDUCTION OF MAMMARY TUMORS IN EXPERIMENTAL ANIMALS

17. LONG-TERM EFFECTS OF INTERNAL IRRADIATION OF ENDOCRINE SYSTEM IN FEMALE RATS.

Dedov VI
Inst. Advanced Training for Physicians, Moscow, USSR
Izv Akad Nauk SSSR [Biol]; (3):454-458 1982

The long-term effects of internal irradiation of the endocrine system were studied in random-bred female rats. The animals received single iv injection of 75Se-selenomethionine (SM: 1.22 x 10(4) becquerel/g). The absorbed doses were 50 rads in the whole body and in the ovaries and 100 rads in the pituitary gland, thyroid, and adrenals. Animals were sacrificed on day 2 of the diestrus 1 and 2 wk, 1, 3, 6, 9, 12, and 18 mo after SM administration. Prolonged internal irradiation induced permanent estrus in 60% of the female rats. The female rats with permanent estrus developed mammary gland neoplasms (the latent period of mammary gland tumors was 5.5-7 mo for mature rats and 2.5 mo for old rats), thyroid and adrenal adenomas, pituitary gland prolactinomas, and uterine polyps. Development of endocrine neoplasms was associated with SM-induced elevation of blood levels of estrogens and prolactin and deficiency of thyroxine. (13 Refs) (In RUS)

18. DOSE-EFFECT RELATIONS FOR INDUCTION OF MALIGNANT AND BENIGN TUMOURS IN THE RAT MAMMARY GLAND (MEETING ABSTRACT).

Broerse JJ, Hennen LA, Van Zwieten MJ, Hollander CF
Radiobiological Institute TNO, Rijswik, The Netherlands
Int J Radiat Biol; 42(1):74 1982

The gross observations and histological classification of mammary tumors induced in three rat strains (WAG/Rij, BN/BiRij and Sprague Dawley) after single dose and fractionated irradiation with x-ray and neutrons of different energies, have been completed for approximately 6000 rats. The number of animals surviving without evidence of tumor as a function of age was established with actuarial statistics. Dose-effect relations were determined by the scoring of the cumulative prevalence at 22 months of age and by the forward shift of tumor appearance with increasing dose. The values for the relative biological effectiveness (rbe) derived from these curves are highest for 0.5 MeV neutrons. In the BN/BiRij and Sprague Dawley rats relatively few carcinomas were observed. For benign tumors in these strains, rbe values of 13 and 5 are obtained for BN/BiRij and Sprague Dawley rats, respectively, at an absorbed dose of 60 mGy 0.5 MeV neutrons. Only for WAG/Rij rats could rbe values be established for the induction of both benign and malignant mammary tumors. For 0.5 MeV neutrons at a dose level of 60 mGy the approximate rbe values are 20 and 15 for benign and malignant tumors, respectively. The dose-effect relations for induction of carcinomas do not indicate a significant increase in rbe for 0.5 MeV neutrons for doses below 60 mGy. A preliminary analysis shows that for equal total doses the fractionated irradiations are as effective as single doses, or even more so, for the induction of mammary tumors. (no Refs)

19. FURTHER STUDIES ON THE RELATIONSHIP BETWEEN ALLOTRANSPLANTABILITY AND THE PRESENCE OF THE CELL SURFACE GLYCOPROTEIN EPIGLYCANIN IN THE TA3-MM MOUSE MAMMARY CARCINOMA ASCITES CELL.

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JNCI; 68(6):981-988 1982

The loss of strain specificity in the TA-St mammary carcinoma ascites cell during passage in ascites form in diseased syngeneic strain A mice was confirmed by the observation that TA3-MM/2 ascites cells were capable of progressive growth in seven foreign mouse strains. Support for the hypothesis that allotransplantability in the TA3-MM lines may be due to masking of cell surface histocompatibility H-2 7a 1 antigens by large glycoprotein (epiglycanin) molecules was obtained from the finding that the capacity of the TA3-MM/2 ascites cell to absorb anti-H-2 7a 1 antibody was several times less than that of the parent TA3-St ascites cell, although it was greater than the capacity of the non-strain-specific TA3-Ha line. Further support for the location of epiglycanin molecules at the cell surface was obtained by transmission electron-microscopic observation of a high concentration of filamentous structures, usually 20-40 nm long, but often extending to 200-300 nm length at the TA3-MM/2 cell surface. Similar structures were also observed at the TA3-Ha cell surface but were not observed at the surface of the TA3-St ascites cell, a cell known to contain no detectable epiglycanin. Epiglycanin molecules, obtained by two different methods from TA3-MM/1, TA3-MM/2, and TA3-Ha ascites cells, were shown to be similar with respect to their capacities to inhibit the binding of 125I-labeled epiglycanin to its antibody, induced in the rabbit by TA3-Ha ascites cells in a radioimmunoassay. (Author abstract) (21 Refs)

20. THE UNIQUE ASSOCIATION OF ALANINE AMINOTRANSFERASE WITH THE TRANSPLANTABLE R323OAC-L ADENOCARCINOMA IN THE FISCHER RAT.

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Diss Abstr Int [B]; 42(6):2315-B 1981

The Research 3230 Adenocarcinoma, Lung subline (R323OAC-L), in the Fischer 344 rat is a transplantable mammary tumor. When placed beneath the kidney capsule, it metastasized readily to the lung causing asphyxiation and death within 6 weeks of implantation. Associated with the growing tumor load was an elevation of serum levels of alanine aminotransferase (ALT), an enzyme considered specific for indicating hepatic damage. Grossly, microscopically and ultrastructurally, there was no indication of hepatic change or damage in tumor-bearing rats. Further serum clinical chemistry tests also confirmed the absence of hepatic damage. The R323OAC-L tumor, metastases and liver from tumor-bearing rats were homogenized then analyzed for ALT activity along with serum from the same rats. Serum and liver homogenates from control rats were also analyzed for the enzyme. Tumor tissue contained approximately one fourth the activity of ALT found in liver tissue. Tumor tissue by weight was approximately 3 times the liver. Despite the lower activity of enzyme per gram of tumor tissue, the R323OAC-L tumor was considered responsible for the increased serum levels of ALT based on the greater amount of tumor tissue and the fact that, being necrotic, the tumor could have been leaking enzyme constantly into the circulation. Starch gel electrophoresis was performed to compare ALT from the primary tumor, metastatic nodules, liver and serum of tumor-bearing rats and liver and serum of control rats. No differences were seen. It was concluded that the enzyme in the tumor tissues was very similar, if not identical, to the ALT produced by the liver. (no Refs)

MECHANISMS AND MODIFICATION OF MAMMARY GLAND CARCINOGENESIS

21. DOSE-RESPONSE STUDIES ON THE INHIBITION OF EXPERIMENTAL MAMMARY, COLON, AND LIVER CARCINOGENESIS BY BUTYLATED HYDROXYTOLUENE (BHT) (MEETING ABSTRACT).

Cohen LA, Reddy BS, Williams GM, Furuya K, Maeura Y, Silverman J, Weisburger JH
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Proc Am Assoc Cancer Res; 23:358 1982

Phenolic antioxidants such as BHT inhibit carcinogenesis at several target organs including breast, colon, liver, lung, and stomach. We investigated (1) whether a dose response relationship exists between the tumor inhibiting effect and BHT level, and (2) whether the inhibiting is influenced by the dose of initiating carcinogen in three well-characterized model systems: the dimethyl-benz(a)anthracene (DMBA)-induced mammary carcinoma, the azoxymethane-induced colon carcinoma, and the 2-acetylaminofluorene (2-AAF)-induced hepatocarcinoma. Two appropriate doses of initiating carcinogen were used and BHT was fed in the diet at concentrations of 6000, 3000, 1000, and 300 ppm. In mammary carcinogenesis, tumor incidence was 75% and 55% and tumor multiplicity 2.5 and 1, respectively, at high (15 mg) and low (5 mg total) dose DMBA. With the high DMBA dose, tumor incidence and multiplicity were significantly inhibited only at the highest level of BHT. At low DMBA dose, tumor incidence and multiplicity were inhibited at all levels of BHT. In colon carcinogenesis, at the high dose of azoxymethane, inhibition as determined by endoscopy was evident at the two higher doses of BHT. In the liver model, 6 weeks of feeding 0.02% AAF produced 26 preneoplastic foci/cm2 liver, identified by resistance to iron accumulation. Concurrent feeding of BHT produced a dose-dependent inhibition of foci production. Thus, BHT exerts a dose-dependent inhibition of carcinogenesis in all three model systems. (no Refs)

22. RETINOIDS AS CHEMOPREVENTIVE AND ANTICANCER AGENTS IN INTACT ANIMALS (REVIEW).

Hill DL, Grubbs CJ
Southern Res. Inst., Box 3307-A, Birmingham, AL, 35255
Anticancer Res; 2(1/2):111-124 1982

Certain retinoids have prevented induction of cancer by carcinogens in the skin, mammary gland, and urinary bladder of experimental animals. In isolated experiments retinoids have also shown anticancer activity against esophageal, cervical, and hepatic cancers. No conclusive evidence of prophylactic activity against cancers of the lung or colon has been found. Retinoids have shown modest activity against those established cancers that are immunogenic. Retinoids apparently have antipromoting and general immunostimulative activities. (137 Refs)

23. EFFECTS OF SELENIUM ON MOUSE MAMMARY TUMORIGENESIS AND GLUTATHIONE PEROXIDASE ACTIVITY.

Medina D, Lane H, Shepherd F
Baylor Coll. Medicine, Houston, TX, 77030
Anticancer Res; 1(6):377-382 1981

Effects of selenium (SeO_2, and Na_2SeO_3) were examined on the tumor-producing capabilities of CV-7 line, 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumorigenesis in BALB/c female mice, and mammary glands of mice which had been hormonally stimulated prior to DMBA treatment. Selenite supplementation reduced the incidence of CV-7 mammary tumors from 70% (21/30) to 20% (6/30) over a period of 38 wk. Further appearance of tumors in the selenite-treated mice was markedly delayed. Samples of normal mammary gland and preneoplastic nodule outgrowth tissues were removed for glutathione-peroxidase (GSH-Px) activity 22 wk after transplantation when the mammary tumor incidences in the control and selenite-treated mice were 47 and 7%, respectively. Preneoplastic tissue had twice the amount of GSH-Px activity than normal mammary gland in both normal and selenite-treated groups. No indication was observed that the expression of murine mammary tumor virus proteins in the preneoplastic tissues were qualitatively different in selenite-treated mice. Selenite at 7 and 10.5 ppm reduced the incidence of DMBA-induced mammary tumors from 55% to 5 and 10%, respectively. In hormone pretreated mice, DMBA-induced tumors arose over a period of 54 wk after carcinogen treatment. Selenite reduced the incidence of mammary tumors from 37 to 14%. Results demonstrated that selenium, in the form of inorganic selenite, is a potent chemoprotective agent for both viral and chemical carcinogen-induced mouse mammary tumorigenesis. (35 Refs)

24. PLASMA PROLACTIN (PRL) AND ITS METABOLIC CLEARANCE RATE (MCR) IN MALE AND FEMALE RATS FED 5 AND 20% DIETARY FATS (MEETING ABSTRACT).

Clinton SK, Mulloy AL, Visek WJ
University of Illinois, Urbana, IL, 61801
Fed Proc; 41(3):357 1982

It has been proposed that prolactin mediates the enhancement of mammary carcinogenesis by dietary fat. We have studied the effect of dietary fat level (10 and 40% of calories as corn oil) on plasma immunoreactive PRL and its MCR in male and female Sprague-Dawley rats. Rats were assigned to modified AIN diets at weaning. After 10 weeks, 15 rats per treatment were decapitated and trunk blood was assayed for PRL by radioimmunoassay. For the MCR studies 10 male and female rats per diet were anesthetized with pentobarbital, fitted with a jugular cannula and treated with 2-bromo-alpha-9 ergocryptine prior to receiving an exogenous bolus of PRL and collection of sequential blood samples to determine PRL clearance. There was no significant effect of fat on plasma PRL (ng/ml) in females at metestrus-diestrus [23 on low fat (LF) vs 17 on high fat (HF)] or proestrus-estrus [339 (LF) vs 329 (HF)]. There was also no significant difference in plasma PRL in male rats fed LF (39) vs those fed HF (55). Although male rats show a higher MCR than females there was no significant effect of fat. The MCR for males was .80 ml/min on LF and .76 mg/min on HF. The MCR for female rats was .36 and .42 respectively. The PRL and MCR data fail to show that dietary fat significantly changes the plasma PRL levels or its MCR. (no Refs)

25. REVERSION OF HUMAN MAMMARY CARCINOMA TO NORMAL EPITHELIAL CELLS (MEETING ABSTRACT).

Hakim AA
University of Illinois at the Medical Center, Chicago, IL
148th National Meeting of the American Association for the Advancement of Science, January 3-8, 1982, Washington, D.C. American Association for the Advancement of Science 182 pp., 1982.

There is a strong relationship between anchorage independence, ie ability to grow unattached, and the tumorigenic properties of cells. The adhesion of cultured fibroblasts or epithelial cells is mediated by fibronectin and/or laminin, respectively. Reduction of cell-surface fibronectin or laminin correlates with the ability of the transformed cells to produce tumor and metastasize. In the present studies, human carcinoma cells (HMCC), and normal mammary epithelial cells (HNMEC) were cultured in presence and absence of graded amounts of fibronectin (Fn), laminin (Ln), dibutyryl-cyclic AMP and adenosine triphosphate (ATP), each alone and combined, for series of subcultures. At each subculture, the cells were examined for the following parameters: Oncogenicity in athymic Nu/Nu mice, agglutinability by concanavalin A, release of plasminogen activator (PA) and glutamyl-transpeptidase (GTase), and by electron microscope. After five subcultures in media supplemented with Fn, Ln and db-cyclic-AMP, HMCC cells progressively lost their oncogenicity and reverted to normal mammary epithelial cell characteristics. Under all experimental conditions, NNMEC cells released statistically non-significant PA and GTase. During reversion of HMCC these released enzyme activities decreased to Nil. (no Refs)

26. EFFECT OF N-(4-HYDROXYPHENYL)RETINAMIDE ON FOOD INTAKE AND GROWTH IN RATS (MEETING ABSTRACT).

Radcliffe JD, Moon RC
Illinois Institute of Technology Research Institute, Chicago, IL, 60616
Fed Proc; 41(3):357 1982

N-(4-hydroxyphenyl)retinamide (HPR) has an anti-proliferative effect on rat mammary epithelium that may be involved in HPR inhibition of mammary carcinogenesis. Body weight gain is reduced during the first week of HPR feeding. An experiment was initiated to determine whether this is due to reduced food intake and if so, how this might modify the effect of HPR on the mammary gland. Retinoid levels in mammary gland and body fat were also determined. Female SD rats (mean wt 176g) were used. Group A was fed, ab lib, a diet containing HPR (782 mg/kg diet). Groups B and C were fed placebo diet: B was fed ab lib and C was pair-fed to A. From age 58-65 days, food intake was lower for A (12.6g/rat/day) than for B (17.3g/rat/day). Group A failed to gain weight, but B gained 19g. After 66 days, food intake was similar in both groups. Final mean body weight (215 days of age) was similar for all groups (283-288g). Mammary glands of groups B and C were similar, but glands of group A showed decreased ductal branching and end bud proliferation. HPR levels in mammary gland and perirenal fat were 10.5 and 21.0 mg/g tissue, respectively. Initial reduction in body weight gain in HPR fed animals is due to reduced food intake which does not affect the anti-proliferative effect of HPR on mammary epithelium. (no Refs)

27. PRELIMINARY CHARACTERIZATION OF MALIGNANT MAMMARY CELL GROWTH INHIBITORS IN NORMAL HUMAN SERUM.

Pigott DA
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Diss Abstr Int [B]; 42(7):2724-B 1982

Plasma-derived human serum (PDS) from normal donors inhibits the growth of the human mammary carcinoma cell line, MCF-7. The growth of HBL-100 cells, a line derived from normal mammary tissue, is not affected. Fractionation of PDS reveals three components responsible for specific inhibition of MCF-7 cell proliferation. Two additional components inhibit proliferation of both cell types. Preliminary characterization of the MCF-7 specific activities indicates the involvement of an IgG and two proteins of molecular weight 70,000 and 50,000 daltons. Non-specific activity is attributable to a lipid component and a 20,000 MW protein. Some evidence exists which indicates a possible relationship between the 70-, 50-, and 20,000 MW proteins. In addition, mitigation of the MCF-7 specific activities is demonstrated by a component(s) also present in PDS. These results indicate that malignant cell proliferation in vivo could be subject to constraints beyond the classical antibody and cell-mediated tumor-immune responses. (no Refs)

28. COMPARISON AND CHARACTERIZATION OF THE ANTITUMOR PROPERTIES OF GAMMA INTERFERON AND TUMOR NECROSIS FACTOR IN THE RAT SYSTEM (MEETING ABSTRACT).

Germain-de Matteis F, Burleson GR
University of Notre Dame, Notre Dame, IN, 46556
Fed Proc; 41(3):442 1982

These studies were designed so as to compare and characterize tumor necrosis factor (TNF) and gamma interferon (IFNgamma) in the rat. TNF was produced in Lou M rats by intravenous (iv) sensitization with Mycobacterium bovis strain BCG, followed by induction by iv injection of endotoxin. IFN-gamma was produced in Lou M rats by iv sensitization with BCG followed by induction with old tuberculin iv. TNF and IFNgamma were compared and characterized with respect to the following: (a) stability at pH, (b) inactivation at 56 C, (c) inactivation by treatment with trypsin, (d) molecular weight determination using sodium dodecyl sulfate polyacrylamide gel electrophoresis, and (e) elution patterns on two affinity chromatography matrices - phenyl sepharose and blue sepharose. The fractions from the columns were monitored for protein, antiviral, TNF, and antitumor activity. TNF and IFNgamma antitumor activity was assayed by a modified dye elution method using a rat mammary adenocarcinoma cell line obtained from dimethylbenzanthracene (DMBA)-induced Sprague Dawley rats. This is the first study comparing and characterizing TNF and IFNgamma in the rat system. Characterization of the antitumor properties of these rat lymphokines will permit the utilization of the excellent rat tumor model system available, so as to assess the antitumor effect of these lymphokines in vivo. (no Refs)

29. PRODUCTION, CHARACTERIZATION, AND ANTITUMOR PROPERTIES OF RAT INTERFERONS (MEETING ABSTRACT).

Burleson GR, Germain-de Matteis F, Herzog DP
University of Notre Dame, Notre Dame, IN, 46556
Fed Proc; 41(3):442 1982

Systems have been developed to optimize the production of rat interferons (IFNs). Kinetic studies and dose-response curves were examined in each of the following systems. Type I (alpha/beta) IFN was produced in a rat cell line induced with Newcastle disease virus. Type II (gamma) IFN was produced from (a) rat spleen cells exposed to Staphylococcal enterotoxin A (mitogen-induced gamma IFN) and (b) rats sensitized by intravenous injection of Mycobacterium bovis, strain BCG, followed by induction 3 weeks later with old tuberculin (antigen-specific gamma IFN). The IFNs were characterized by pH 2 sensitivity, stability at 56 C, and susceptibility to treatment with trypsin. The IFNs were also compared and further characterized by their elution patterns on 5 different affinity chromatography matrices. The elution profiles were monitored for protein, antiviral, and antitumor activities. The antiviral activity was measured by means of a microtiter CPE-inhibition assay, using vesicular stomatitis virus. The antitumor activity was determined by measuring the growth inhibitory effect of the IFNs on a rat mammary adenocarcinoma cell line using a microtiter dye elution assay. (no Refs)

HORMONAL ASPECTS OF MAMMARY GLAND CANCER

30. HORMONE DEPENDENCY IN N-NITROSOMETHYLUREA-INDUCED RAT MAMMARY TUMORS.

Arafah BM, Finegan HM, Roe J, Manni A, Pearson OH
Dept. Medicine, Case Western Reserve Univ. Sch. Medicine, Cleveland, OH, 44106
Endocrinology; 111(2):584-538 1982

The majority (87%) of N-nitrosomethylurea-induced rat mammary tumors regressed within 1 wk after hypophysectomy (hypox). After a hypox-induced tumor regression, ovine PRL (oPRL), and 17beta-estradiol (E2) were administered separately or in combination in order to define the individual role of these hormones in regulating tumor growth and influencing estrogen (E), progesterone (Pg), and PRL receptor (R) levels. Administration of E2 (2.5 ug twice daily) or oPRL (20 IU daily, started 5 days after hypox and continued for 10 days), resulted in stabilization of tumor growth. Simultaneous administration of E2 and oPRL resulted in a synergistic effect and reactivation of tumor growth. ER levels in mammary tumors were significantly lower than those in the control 15 days after hypox (p less than 0.01). Treatment with E2, oPRL, or both simultaneously had no significant effect on ER levels. A significant decline in PgR levels was noted at both 5 and 15 days after hypox. Whereas treatment with oPRL had no significant effect on PgR levels, E2 administration either alone or in combination with oPRL restored PgR levels to control values. PRLR levels were unchanged from control values at 5 days, but significantly declined (p less than 0.005) 15 days after hypox. Treatment with E2, oPRL, or both hormones simultaneously partially maintained PRLR and prevented the decline to the extremely low level noted in the untreated group. We conclude that the growth of nitrosomethylurea-induced rat mammary tumors is dependent on both E2 and PRL. There was a synergistic effect between E2 and PRL on tumor growth but not on ER, PgR, or PRLR. Neither E2 nor PRL had any significant effect on ER after hypox. PgR is under E2 control. Either E2 or PRL or both hormones were able to maintain PRLR in mammary tumors after hypox. (Author abstract) (17 Refs)

31. ESTROGEN AND PROGESTERONE RECEPTORS IN BREAST CANCER IN BLACK AMERICANS. CORRELATION OF RECEPTOR DATA WITH TUMOR DIFFERENTIATION.

Mohla S, Sampson CC, Khan T, Enterline JP, Leffall L, White JE, Gabriel BW, Hunter JB
Howard Univ. Cancer Center, 2041 Georgia Ave., Northwest, Washington, DC, 20060
Cancer; 50(3):552-559 1982

It has been observed that 60-70% of breast cancer patients have estrogen (ER) and that nearly two-thirds of such patients respond favorably to endocrine therapy. Cytosolic ER and progesterone receptors (PgR) have been evaluated in the current study, among 146 black women with breast cancer in order to determine whether the distribution of ER and PgR differs from the national normal. The results showed following trends that were similar to reports from other institutions: (1) postmenopausal patients and primary tumors showed higher ER positivity than premenopausal patients and metastatic sites, respectively; (2) a significant correlation between the ER positivity and tumor grade; and (3) a higher PgR positivity in ER-positive patients than in ER-negative patients. However, statistically significant differences were observed in three parameters when compared to reports from other institutions on white patients: (1) a low incidence of ER-positive (46%) and high incidence of ER-negative (42%) tumors; (2) a higher incidence of poorly differentiated (55.5%) and a lower incidence of well differentiated (5.5%) tumors; tumor grade was independent of age, menopausal status, histopathology and stage; and (3) a higher percentage of patients discovered at a more advanced stage of the disease. The clinical implications of these results in explaining the relatively poorer survival of black women with breast cancer compared to whites is discussed. Whether this high incidence of PD tumors and thus a high incidence of ER negativity is due to ethnic differences and/or environmental and other factors remains to be elucidated. (Author abstract) (48 Refs)

32. ROLE OF ESTROGEN AND PROLACTIN IN THE GROWTH AND RECEPTOR LEVELS OF N-NITROSOMETHYLUREA-INDUCED RAT MAMMARY TUMORS.

Manni A, Rainieri J, Arafah BM, Finegan HM, Pearson OH
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Cancer Res; 42(9):3492-3495 1982

Forty-eight of 81 (59%) of N-nitrosomethylurea-induced rat mammary tumors regressed in av to almost one-half of the original size 10 days after ovariectomy (ovax) (hormone responsive), while 33 remained essentially unchanged (hormone resistant). At 20 days after ovax, further decline in hormone-responsive tumors was observed when the rats were treated daily with 0.9% NaCl soln on the 10th day after ovax. Treatment for the same length of time with estrogen either alone or in combination with bromocriptine (to effectively suppress serum prolactin level) prevented tumor regression in hormone-responsive tumors. A similar effect was observed when rats were treated with perphenazine (to stimulate endogenous prolactin secretion) either alone or in combination with the antiestrogen tamoxifen. Estrogen receptors (ERs) significantly declined after ovax. Treatment with estrogen or perphanazine did not have any significant effect on ER levels. Progesterone receptors (PGRs) became virtually undetectable after ovax. Treatments with estrogen, estrogen plus bromocriptine, and perphenazine plus tamoxifen but not perphenazine alone were able to partially restore PGRs although this effect was of borderline statistical significance. ER and PGR levels were not significantly different between hormone-responsive and -resistant tumors within each group. We conclude that both estrogen and prolactin play a role in the growth of the N-nitrosomethylurea-induced rat mammary tumor. Changes in ER and PGR levels did not correlate with tumor growth under the present experimental conditions. (Author abstract) (18 Refs)

33. METABOLISM OF TESTOSTERONE BY GR MOUSE MAMMARY TUMORS.

Abul-Hajj YJ, Kiang DT
Dept. Pharmaceutical Cell Biology, Univ. Minnesota, Coll. Pharmacy, Minneapolis, MN, 55455
Cancer Res; 42(9):3510-3513 1982

The metabolism of testosterone by GR mouse mammary tumors following serial transplantation was studied. Oophorectomized female recipients were maintained on estrone and progesterone (OEP) or without hormone maintenance (oophorectomized-only group) in order to assess whether the growth of the tumor was hormone dependent (HD) or hormone independent (HI). Tumors in the early generations of the OEP group were HD (generations 1 to 4), which became HI in the latter generations (G5 to G18). All tumors developed in the oophorectomized-only group (generations 1 to 18) were HI. All tumors investigated were capable of metabolizing testosterone to 4-androstenedione, 16alpha-hydroxytestosterone, 5alpha-dihydrotestosterone, 5alpha-androstanedione, and 5alpha-androstanediol. Total 5alpha-reduction in OEP group ranged between 50 and 60% of neutral metabolites in HD tumors and dropped to 13 to 28% in HI tumors (generations 5 to 18), similar to the activities (20 to 30%) of the HI tumors in the oophorectomized only group. Different patterns of estrogen synthesis were observed among these tumors. Although tumors showed the presence of appreciable amounts of estriol, estrone was synthesized only in 5 of the 9 HI tumors in the oophorectomized only group. The most striking contrast was that estradiol was synthesized by all HI tumors in the oophorectomized-only group and the OEP group but not in the HD tumors. (Author abstract) (13 Refs)

IMMUNOLOGICAL ASPECTS OF MAMMARY GLAND CANCER

34. NATURAL AND INDUCED IMMUNITY TO MOUSE MAMMARY TUMORS AND THE MAMMARY TUMOR VIRUS (MUMTV).

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Springer Semin Immunopathol; 4(4):333-372 1982

Information on immune responses in normal and tumor-bearing hosts either against murine mammary tumor virus (MuMTV) antigens or the actual tumors themselves is discussed and correlation with the possible prophylaxis and therapy of tumors in the mouse mammary tumor model system is made. The cell-mediated immune responses (mostly those mediated by T cells), which can be detected in vivo or in vitro either spontaneously or in immunized mice are reviewed in detail. The unique properties of the MuMTV model and in vivo immunologic studies are discussed. Topics discussed include in vitro cytotoxicity and related phenomena (studies using colony-inhibition assays and microcytotoxicity, antigenic complexities of the system) and studies using cell-mediated cytotoxicity assays (specificity and characteristics of the response, in vivo-in vitro discrepancies, serum factors, T cell interactions, suppressor T cells in MTV-positive mice, the effect of thymectomy, in vitro sensitization, natural cell mediated cytotoxicity in MTV-positive mice and horizontal transmission of MuMTV). Adult thymectomy completely abrogated the suppressive activity in the Lyt-23 fraction of MTV-positive cells, but had no effect on the Lyt-1 helper component. These findings may explain the in vivo effects of thymectomy producing a decline of mammary tumors. Thymectomy at 6 days of age produced a significant decrease in tumor incidence, while thymectomy after 30 days of age had no effect on mammary tumor development in C3H/BiUmc virgin females. (247 Refs)

35. IGA CONTAINING IMMUNE COMPLEXES IN DOGS BEARING A SPONTANEOUS MAMMARY ADENOCARCINOMA.

Balint J, Nagai T, Ikeda Y, Meek K, Terman DS
Dept. Medicine, Baylor College Medicine, Houston, TX, 77030
Clin Exp Immunol; 49(2):433-440 1982

Sera from dogs with mammary adenocarcinoma were assessed for the presence of immune complexes (IC) and the physicochemical composition of these complexes was investigated. Employing 125I-anti-canine IgG as indicator, elevated levels of C1q binding IgG were detected in sera of dogs with mammary adenocarcinoma. Polyacrylamide gel electrophoresis (PAGE) analysis of IC isolated by G-200 fractionation and protein A affinity chromatography revealed the presence of a dense polypeptide band corresponding to the alpha chain of IgA which was present in the mammary adenocarcinoma sera but not in normal dog sera or sera from dogs with other tumors. Employing monospecific radiolabeled anti-canine IgA as indicator in solid phase C1q binding radioimmunoassays, significantly elevated levels of C1q binding IgA were detected in five of eight mammary adenocarcinoma sera but not in sera of normal dogs or other tumor bearing dogs (p less than 0.05). Sera from mammary adenocarcinoma bearing dogs treated with 5% polyethylene glycol (PEG) and subjected to sucrose density gradient ultracentrifugation revealed IgA containing IC in fractions greater than 7S to greater than 19S. Findings suggest that IC are present in sera of dogs with mammary adenocarcinoma and that IgA is a major and unique component of these complexes and, hence, may play a significant role in the development and evolution of the canine immune response to mammary adenocarcinoma. (Author abstract) (24 Refs)

36. PURIFIED MEMBRANE FRACTIONS FROM MAMMARY TUMOR CELLS ELICIT BIOLOGICAL REACTIVITY IN IN VITRO CELL-MEDIATED IMMUNE REACTIONS.

Buessow SC, Caldwell K, Fletcher MA, Lopez DM
Dept. Microbiology, Univ. Miami Sch. Medicine, Miami, FL, 33101
Eur J Cancer Clin Oncol; 18(6):595-604 1982

Lithium chloride (LiCl) aggregation followed by centrifugation through a sucrose step gradient was used to obtain purified plasma membranes from two sublines of mouse mammary adenocarcinoma. These two tumor lines were chemically induced by treatment of a hyperplastic nodule with 7,12-dimethylbenzanthracene (DMBA). One line, D1-DMBA-3, has been found to be immunogenic to the host of origin, while the other, D1-DMBA-2, does not elicit specific tumor immunity as previously tested in in vivo and in vitro immune reactions. The purified membrane fractions were assayed for protein, DNA and sialic acid content as well as enzymatic markers of membrane purity. When tested in blastogenesis and cytotoxicity reactions, membrane-containing fractions from the D1-DMBA-3 immunogenic tumor were found to be stimulatory to spleen cells of D1-DMBA-3 tumor bearers over a 10-fold protein concentration. Spleen cells from normal mice do not respond in these reactions to the various tumor fractions. No reactivity was observed when non-membrane-containing preparations were used as stimuli in the cell-mediated immune reactions. The specificity of these reactivities was further demonstrated by the lack of responses when fractions from the non-immunogenic D1-DMBA-2 tumor were tested in parallel in our in vitro assay. The data presented indicate that the procedure employed is useful for the isolation of membrane-associated, tumor-specific antigens which can be easily quantitated and still retain biological activity in in vitro tests of cell-mediated immunity. (Author abstract) (41 Refs)

VIRAL ASPECTS OF MAMMARY GLAND CANCER

37. HETEROGENEITY IN MOUSE MAMMARY TUMOR CELLS WHEN TRANSFORMED BY BOVINE PAPILLOMAVIRUS (MEETING ABSTRACT).

Henley MJ, Meinke WJ
University of Arizona, Tucson, AZ, 85724
Fed Proc; 41(3):1278 1982

Bovine papillomaviruses (BPV) transform mouse mammary tumor cells. The transformed cells grow in soft agar to form colonies. The viral genome exists as a high copy episome in the nucleus of transformed cells. The transformation index (Ti) of six clones was evaluated over several passages (p) of the cells. Ti equals numbers of colonies which grew in 0.25% agar/ number of cells plated in 0.25% agar. There were significant differences in the Ti values of the clones. Ti values fell into two broad groups regardless of the cell passage number. One group had Ti values ranging from 0.01 to 0.08; the other group had Ti values 5-50 fold higher ranging from 0.30 to 0.50. One clone had a Ti value less than 5 x 10(-5) at p10 while at p20 the Ti was 5 x 10(-2). These data are consistent with the proposal that BPV genomes, present as episomal elements in transformed cells, are segregated unequally at mitosis and therefore confer marked heterogeneity upon the transformed cells as evidenced by their ability to form colonies in agar. To support this hypothesis, further evidence is being obtained using retinoic acid as an inhibitor of BPV-transformed cells to form colonies in agar. Cellular retinoic acid binding protein (CRABP) was below detectable levels in untransformed cells. However, significant amounts of CRABP are found in BPV-transformed cells. Nevertheless, the amount of CRABP varied several fold in the clones examined. (no Refs)

38. CIRCULATING IMMUNE COMPLEXES, ANTIGENS, AND ANTIBODIES RELATED TO THE MURINE MAMMARY TUMOR VIRUS IN C3H MICE.

Dong ZW, Witkin SS, Fernandes G, Sarkar NH, Good RA, Day NK
(c/o Day), Oklahoma Medical Res. Foundation, 825 N.E. 13th St., Oklahoma City, OK, 73104
J Immunol; 129(2):872-876 1982

A comparative study was performed to measure levels of free antibody to MuMTV, MuMTV membrane antigen (gp52), and antigen-antibody complexes in sera of mammary tumor-bearing and age-matched non-tumor bearing C3H/Bi mice. Approx 90% of these mice spontaneously develop breast cancer. Levels of MuMTV antibody and C3-containing circulating immune complexes (CIC) were highest in the sera of the mice without overt evidence of breast cancer. MuMTV gp52 antigen was present in higher concentrations in the sera of mice with overt breast cancer. Fractionation of the sera on sucrose gradients followed by analysis for CIC confirmed that levels of C-containing CIC were lower in sera from mice with tumors than in nontumor bearers. The CIC were, however, of smaller size in sera of tumor-bearing mice. When the sera were assayed for CIC by an assay in which C binding does not compete with binding of CIC to the sperm, the levels of these small-sized CIC in sera of mice with breast cancer were now comparable to CIC levels in nontumor-bearing mice. MuMTV antibody was located in both 7S and high mw regions of the gradients. To determine whether the CIC contained MuMTV antigen, the CIC were bound to bull sperm Fc receptors and assayed for reactivity with monospecific goat anti-gp521gG. Significantly higher levels of reactivity to anti-gp52 were detected in CIC from C3H mice than in CIC from sera of age-matched AKR mice with or without leukemia or from MRL/MpJ-lpr/lpr mice. These data indicate that there is a shift from MuMTV antibody excess to MuMTV antigen excess and from larger C-fixing CIC to smaller non-C-fixing CIC after appearance of overt breast cancer in C3H mice. (26 Refs)

39. RELATIONSHIPS BETWEEN MORPHOLOGY AND VIRAL ETIOLOGY IN MAMMARY TUMORS OF BALB/CFC3H AND BALB/CFRIII MICE.

Pingitore R, Squartini F
Istituto di Anatomia Patologica, Scuola Medica, Via Roma 57, 56100 Pisa, Italy
Tumori; 68(3):199-203 1982

The morphologic patterns of mammary tumors induced by milk-transmitted C3H and RIII murine mammary tumor viruses (MuMTVs) in BALB/c hosts infected by foster nursing were investigated further and compared taking into account several tumor and host variables. Comparison of BALB/cfC3H and BALB/cfRIII mammary tumors under identical tumor and host conditions showed highly significant differences in subgross morphology and histologic structure. Differences in cytology were also observed. Data suggest that mammary tumor morphology in high cancer strain mice is controlled by the causative MuMTV. (Author abstract) (14 Refs)

40. COMPARISON OF MAMMARY TUMORIGENESIS BETWEEN LITTERS IN RELATION TO MAMMARY TUMOR VIRUS ANTIGENIC EXPRESSION IN THE MILK OF C3H/HE MICE.

Nagasawa H, Nakajima Y, Morimoto J, Imai S, Tsubura Y
Experimental Animal Res. Lab., Meiji Univ., Tama-ku, Kawasaki,, Kanagawa 214, Japan
Life Sci; 31(1):83-88 1982

As a possible step to estimate the relationship between mammary tumor virus (MTV) and mammary tumorigenesis in mice, MTV antigenic expression in mother's milk and spontaneous mammary tumorigenesis in their daughters were compared between the first, the second and the third litters of the highly inbred strains of C3H/He mice with low mammary tumor incidence. While MTV antigenic expression was detected in all undiluted samples at each litter by immunodiffusion test, the amount of antigen as measured by the single radial immunodiffusion method was increased with increasing litter numbers. On the other hand, the development of preneoplastic mammary hyperplastic alveolar nodules was different little between litters and mammary tumor incidence by 13 mo of age was very low with no difference in all litters. The pattern of estrous cycles and plasma prolactin level were also similar in each litter. The results suggest that spontaneous mammary tumorigenesis in mice is not always affected quantitatively by the amount of MTV when endocrine and genetical conditions are similar. (Author abstract) (19 Refs)

41. THE GLUCOCORTICOID HORMONE REGULATED MURINE MAMMARY TUMOR VIRUS TRANSCRIPTION UNIT.

Ucker DS
University of California, San Francisco, CA
Diss Abstr Int [B]; 42(10):3925-B 1982

The glucocorticoid receptor protein, complexed with an active ligand such as dexamethasone, selectively stimulates the transcription of murine mammary tumor virus (MTV) sequences integrated into the genome of cultured rat hepatoma (HTC) cells. Analyses of transcriptional rates of proviral and flanking cellular sequences, and in corresponding 'preinsertion fragments' have revealed that the region of the cellular genome into which an MTV provirus integrates need not itself be either transcriptionally active or hormonally responsive. Thus hormonal regulation of viral transcription appears to reflect the presence of regulatory sequences within the MTV DNA itself. Using a line of infected HTC cells that produces a detectable basal level of MTV RNA, we have compared the structure of MTV transcripts synthesized in hormone treated and untreated cells. Two species of MTC transcripts (7.8kb and 3.8kb) are produced in the absence of dexamethasone, and both species are proportionally induced in its presence; moreover, the 5' termini and polyA addition sites of these transcripts are identical and are not altered by hormonal induction. The 5' terminus of nascent MTV RNA is indistinguishable from that of mature viral mRNA, is independent of the proviral integration site, and maps to the sequence at the 5' terminus of virion RNA residing in the MTV long terminal repeat (LTR). The concentration of 5' MTV termini in nascent transcripts increased rapidly upon dexamethasone treatment. The concentration of 3' termini increases in similar fashion, albeit lagging seven minutes behind 5' termini induction. This lag reflects the transit time for RNA polymerase II across the MTV transcription unit. In vitro labelling of the nascent chains by runoff transcription indicates that the specific increase in the rate of MTV RNA synthesis is half maximal within nine minutes of hormone addition. Therefore, basal synthesis of MTV RNA in these cells appears to be initiated at a single site within the MTV LTR, and dexamethasone rapidly stimulates expression from that same site. (no Refs)

42. REGULATORY AND CODING POTENTIAL OF THE MOUSE MAMMARY TUMOR VIRUS GENOME.

Donehower LA
George Washington University, Washington, DC
Diss Abstr Int [B]; 42(10):3946-B 1982

In order to study the structural basis of mouse mammary tumor virus (MMTV) integration and transcriptional regulation. DNA from a cell line derived from C3H/HeN mouse mammary carcinoma was utilized to molecularly clone integrated MMTV proviruses and adjacent cellular sequences. The mammary carcinoma cell line, 34i, contained approximately 20-25 newly acquired proviruses through infection and at least three endogenous MMTV proviruses present in the genomes of all C3H/HeN mice. Molecular cloning in the lambda vector phage, Charon 4A generated clones containing only the 3' half of integrated exogenous MMTV proviruses and endogenous MMTV Unit II. The nucleotide sequence of the long terminal redundancy (LTR) of the exogenous and endogenous Unit II proviruses was determined. In addition, four 3' virus-cell joint regions representing four independent integration events were sequenced. There was no apparent sequence homology among the cellular sequences and between the cellular sequences and MMTV sequences, confirming that there is no apparent cellular sequence specificity with respect to MMTV integration. Specificity of integration with respect to the viral sequences, however, was absolutely precise. The sequence of the exogenous MMTV LTR was 1323 base pairs in length. The position of possible RNA polymerase II initiation and termination signals in both LTRs corresponded closely to the expected regions of viral RNA initiation and termination specified by current models. Both exogenous and endogenous LTRs contained a large translational open reading frame, with sufficient information for a protein of 198 and 199 amino acids, respectively. (no Refs)

43. MOUSE MAMMARY TUMOR VIRUS GENE EXPRESSION: REGULATION VIA CHROMATIN STRUCTURE AND GLUCOCORTICOID HORMONES.

Feinstein SC
University of California, San Francisco, CA
Diss Abstr Int [B]; 42(10):4044-B 1982

Two mammary tumor virus (MTV) proviruses, integrated at different chromosomal loci in the genome of two clonal isolates of cultured rat hepatoma (HTC) cells, were investigated. One cell line, J2.17, epxresses MTV RNA only in the presence of glucocorticoid hormones, whereas proviral genes in the other line, J2.15, are not transcribed in the presence or absence of glucocorticoids; nonetheless, proviral genes and cellular components that mediate hormone responses appear intact and normal. Mild DNase I digestion of chromosomes in isolated nuclei reveals that the J2.17 MTV DNA sequences are packaged in highly DNase I sensitive chromatin, whereas J2.15 MTV chromatin is relatively nuclease resistant. These results demonstrate that the same genetic element, located at two different chromosomal loci within a single cell, can differ in both chromatin structure and gene expression. Analysis of the chromatin structure of appropriate DNA sequences in uninfected HTC cells suggests that the differences in the chromatin structure of the two proviruses reflects a 'spreading effect', in which integrating DNA is packaged into chromatin similar in configuration to surrounding chromatin. Thus, it is proposed that chromosomal position determines the folding pattern of newly introduced DNA sequences; this pattern in turn determines whether the genes can subsequently transcribe in response to the hormonal inducing signal. (no Refs)

BIOCHEMICAL, PHYSIOLOGICAL, MORPHOLOGICAL AND OTHER ASPECTS OF BREAST CANCER

44. COMPARATIVE IMMUNOHISTOCHEMICAL LOCALIZATION OF FIBRONECTIN AND ACTIN IN HUMAN BREAST TUMOR CELLS IN VIVO AND IN VITRO. I. FIBROADENOMA.

Gilbert MA, Noel P, Faucon M, De Ceccatty MP
Unite de Morphologie Cellulaire et Tissulaire, Centre Leon Berard, 28 Rue Laennec, F-69373 Lyon Cedex, France
Virchows Arch [Cell Pathol]; 40(1):99-112 1982

The presence and distribution of fibronectin and actin in breast fibroadenoma cells have been investigated in frozen sections and primocultures of the same samples, by means of indirect immunofluorescence techniques. In the tissue cells, epithelial cells were negative whereas myoepithelial cells were positive with the two antibodies. Moreover, fibronectin was mainly distributed in basal lamina of ducts and ductules whereas actin appeared to label stroma cells. In primocultures obtained from the same samples of fibroadenomas, the labeled patterns of fibronectin and actin were not really distinguishable between cells; the two protein distributions were quite usual. Our data on human breast fibroadenoma cells are in agreement with the concepts of cellular adaptation or selection in culture and emphasize the difficulty in correlating results of 'in vitro' and 'in vivo' studies. (Author abstract) (41 Refs)

45. CHEMICAL CARCINOGEN ACTIVATION IN THE RAT MAMMARY GLAND: INTRAORGAN CELL SPECIFICITY.

Gould MN
Dept. Human Oncology, Wisconsin Clinical Cancer Center, Univ. Wisconsin, Madison, WI, 53792
Carcinogenesis; 3(6):667-669 1982

Cells from 50-55 day old virgin Sprague-Dawley female rat mammary gland were divided into parenchymal (epithelial) and stromal enriched populations. The ability of these cells to activate carcinogens was quantitated employing a mediated mutagenesis assay. In addition, the populations' ability to produce water soluble metabolites from these carcinogens was estimated. We report that the potent mammary carcinogen 7,12-dimethylbenz[a]anthracene was activated by both mammary parenchymal and stromal cells, while the non-mammary carcinogen aflatoxin B1 was not activated by either cell type. However, the weak mammary carcinogen benzo[a]pyrene was activated by the stromal cells and not by the parenchymal cells from which mammary carcinomas arise. The data suggest that the intra-organ relationship between cell types that activate a carcinogen, and cell types that undergo neoplastic transformation, may in part help explain the organ specific potency of a carcinogen. (Author abstract) (7 Refs)

46. ISOLATION AND CHARACTERIZATION OF A SERIALLY CULTIVATED, NEOPLASTIC, EPITHELIAL CELL LINE FROM THE N-NITROSOMETHYLUREA INDUCED RAT MAMMARY ADENOCARCINOMA.

Cohen LA
American Health Foundation, Naylor Dana Inst. Disease Prevention, Dana Road, Valhalla, NY, 10595
In Vitro; 18(6):565-575 1982

A new in vitro model for human breast cancer is described. Derived from an N-nitrosomethylurea (NMU) induced rat mammary adenocarcinoma, this serially cultivated cell line has been demonstrated, by a variety of criteria, to be an authentic neoplastic, rat mammary epithelial cell line. The criteria used include morphological and growth characteristics; the presence of specific cell surface antigens; steroid hormone receptors; hormone responsiveness; casein production; karyotype and isoenzyme profile analysis; anchorage independent growth and oncogenicity. Inasmuch as the NMU cell line possess high concentrations of glucocorticoid and androgen receptors, it may provide a useful model for study of the action of these hormones in human breast cancer. In addition, the NMU line may serve as a valuable in vitro model in which to assess the effects of a variety of endogenous and exogenous agents known to influence mammary tumor growth in vivo, including drugs, nutrients, and growth factors. (Author abstract) (44 Refs)

47. CELL PROLIFERATION IN FIBROCYSTIC DISEASE AND POSTMENOPAUSAL BREAST DUCTS MEASURED BY THYMIDINE LABELING.

Meyer JS, Connor RE
Dept. Pathology, Jewish Hosp., 216 S. Kingshighway, P. O. Box 14109, St. Louis, MO, 63178
Cancer; 50(4):746-751 1982

The thymidine labeling indexes (TLI) of normal and abnormal epithelium in the human breast were measured in 108 surgical specimens. The mean values for various histologic entities were: normal lobule 0.91%; normal postlobular duct 0.71%; lobular hyperplasia 0.82%; ductal hyperplasia, lobular cell type 0.74%; intraductal hyperplasia 0.79%; papillary intraductal hyperplasia 1.02%; blunt duct adenosis 0.68%; cyst 0.56%; infiltrating carcinoma 6.82%; carcinoma in situ 5.53%. The TLI of the normal lobule declined significantly with increasing age, but that of the normal postlobular duct did not. Before the menopause, the mean TLI of the normal lobule was 1.01%, and that of the normal postlobular duct was 0.75%. After the menopause the values had declined to 0.26% and 0.41%, respectively. These findings indicated that the lobules are more sensitive to stimulation by sex steroids than the postlobular ducts. The TLIs of the various benign proliferative entities were not significantly correlated with age, and like the normal lobule and postlobular duct were near the low end of the range of TLI of breast carcinoma. Benign proliferative entities with TLIs in the high part of the breast carcinoma range were not encountered. (Author abstract) (16 Refs)

48. MORPHOLOGIC CHARACTERISTICS OF C3H/HEJ MOUSE MAMMARY GLAND ADENOCARCINOMAS (MEETING ABSTRACT).

Spring-Mills E, Ames IH
Department of Anatomy and Urology, State University of New York, Syracuse, NY
Anat Rec; 202(3):181A 1982

Mammary adenocarcinomas which developed in C3H/HeJ mice carrying the mammary tumor virus were studied using light, scanning and transmission electron microscopy. Three major cellular patterns were observed either within the same tumor or in different tumors. A solid pattern composed of cords or strands of tumor cells with or without intracytoplasmic lumens interspersed between larger areas of tumor cells arranged in a glandular or alveolar configuration around a central lumen with or without eosinophilic secretion. A lobular pattern containing moderate amounts of stromal tissue subdividing the tumor cells into units resembling large, atypical lobules or gland fields. The secretory units were more variable in size, contained more mitotic figures and cellular hyperplasia than in areas with the solid pattern. A cystic pattern characterized by large epithelial lined spaces containing eosinophilic secretion and few regions with a glandular appearance. Thick, moderately long, irregular microvilli and very short microvilli were present on most cells. Sometimes they occurred in association with apical ridges. Most tumor cells contained large nuclei which varied in contour from smooth to moderately irregular as well as in the amount and distribution of heterochromatin. The cytoplasm varied in composition. Many tumor cells had scattered, small mitochrondria, rudimentary Golgi, few profiles of RER and numerous free ribosomes or polysomes. Others were more specialized and contained more RER as well as lipid droplets, lysosomes, tonofilaments and viral particles. (no Refs)

49. BIOLOGICALLY ACTIVE COMPONENTS OF A PERCHLORIC ACID EXTRACT OF MTV-INDUCED MAMMARY TUMORS (MEETING ABSTRACT).

Laing CA, Japal KM
Howard University Cancer Center, Washington, DC, 20060
Med Pediatr Oncol; 10(1):103 1982

Spleen cells of BALB/c mice inoculated with 1x10(6) viable MTV (mammary tumor virus) induced mammary tumor cells exhibited, in vitro, a biphasic DNA synthetic response to syngeneic antigenic extracts (AMMT) of the tumor isolated by Perchloric Acid extraction. The first phase of the response peaked at 10 or 13 days post inoculation and declined drastically three days thereafter. The second phase appeared 3-6 days after the decline of the first (13-16 days post inoculation) and correlated with ulceration, infection, and central necrosis of the tumor. The response predominantly T-cell mediated. The levels of Theta (Thy 1.2) and Ig positive cells of the spleen differed only slightly from controls at intervals over the 25 day period post inoculation. Macrophage population rose from less than 2% in controls to 12% at appearance of the first peak and persisted through the decline. With ulceration of the tumor the macrophage population rose sharply to exceed 25% by day 25. When spleen cells were depleted of macrophages (so that residual macrophages constituted approximately 2% of the depleted population) and cultured with AMMT, the response was impaired (compared to undepleted cells) over the duration of the first phase. At the decline, depletion of the macrophage population further suppressed the low level of predepletion reactivity seen. At the second phase depletion of macrophages resulted in an enhancement of the response. AMMT eluted into two active fractions (MW 70,000 and 38,000) on LKB ultrogel. Specific activity of the 70,000 MW fraction was increased up to 40 fold above the crude fraction. Thus AMMT is capable of initiating lymphoproliferative response in previously sensitized cells. The response is regulated by macrophages which may exert either a supportive or suppressive role. (no Refs)

50. TRANSMEMBRANE POTENTIAL CHANGE (TPC) OF SENSITIZED HUMAN LEUKOCYTES BINDING ORGAN-SPECIFIC CANCER NEOANTIGENS (OSN) (MEETING ABSTRACT).

Shenouda G, Thomson DM
The Montreal General Hospital Research Institute, Montreal H2G 1A4, Canada
Fed Proc; 41(3):311 1982

In this study we measured the TPC of leukocytes before and after exposure to extracts of the sensitizing or control cancer. The TPC was measured by the uptake of the permeant lipophilic cation [3H-Phenyl]Tetraphenylphosphonium bromide which equilibrates rapidly across biological membranes and the measurement of its distribution reflects the magnitude and direction of TPC. Leukocytes from early breast cancer patients when challenged with the breast OSN showed TPC. Leukocytes from patients with advanced breast cancer showed no TPC when challenged with breast OSN, unless the leukocytes were exposed before to PGE2 5 x 10(-6) M. The TPC was immunologically specific. The mechanism of the TPC was characterized. Monocytes armed with cytophilic antitumor antibody showed TPC when challenged with the sensitizing OSN, whereas T-lymphocytes did not. The TPC of leukocytes consisted of 2 reactions. There is TPC of the armed monocytes when they bind the OSN that occurred in the presence of ETYA or FPL 55712; and there is TPC induced in bystander cells by leukotrienes released from the monocytes when they bind OSN that could be blocked by ETYA or FPL 55712. TPC is an early event in stimulus-response coupling of human leukocytes reacting with their sensitizing cancer extracts. (no Refs)

REVIEWS AND OTHER RELATED STUDIES

51. BASELINE HISTOPATHOLOGY OF NEW FIRST-GENERATION SYRIAN GOLDEN HAMSTER HYBRID USEFUL FOR CARCINOGENESIS BIOASSAY (MEETING ABSTRACT).

Adams RA, Bernfeld P, Homburger F, Soto E, Van Dongen CG
Bio-Research Institute, Cambridge, MA
1st World Congress on Toxicology and Environmental Health, May 27-30, 1982, Washington, D.C. American College of Toxicology 28 pp., 1982.

Chvedoff concluded from studies in 1200 hamsters that 'Syrian hamsters may have advantages over both rats and mice as a test system for evaluation of carcinogenic potential in the rodent life-span bioassay' because of low spontaneous tumor incidence, established susceptibility to carcinogens and relatively low body weight requiring smaller doses than rats. While carcinogen-susceptible BIO F1D Alexander hamsters live significantly longer than either parental strain and therefore are more useful for long-term carcinogenesis bioassay, their spontaneous tumor incidence remains as low as that of the parental strains. The histopathology of these spontaneous tumors reveals them to be principally adrenal carcinomas and lymphomas, with complete absence of the tumor types usually induced by carcinogens, ie, gastrointestinal, mammary, pancreatic, renal and urinary bladder tumors. The sensitivity of the bioassay system (for detection of weak carcinogens) is thereby increased. Death, which occurs earlier in females than in males, appears to be due to nephrotic changes in the kidneys. This was accompanied, in the females, by widespread amyloidosis, not seen in the longer lived males. Grossly noted thickenings of the intestinal wall in cecum and colon were found to be cystic hyperplasias. Atrophy of testes was prevalent and there was an incidence of 4.6% uterine carcinoma, not previously noted in females of the paternal strain. (no Refs)

52. BIOLOGICAL CARCINOGENESIS.

Rich MA, Furmanski F
AMC Cancer Res. Center and Hosp., Lakewood, CO
Biological Carcinogenesis. New York, Marcel Dekker, Inc., 310 pp., 1982.

The general principles which govern carcinogenesis are identified for each of the major classes of carcinogens and the extent these principles are applicable to the carcinogenic process induced by other classes of agents is determined. Current knowledge on the interaction of carcinogens and the identification of biological systems where viral, chemical, and physical carcinogens are demonstrably interactive are described. Mechanisms in viral carcinogenesis are discussed with respect to: T-cell growth, T-cell growth factor, T-cell leukemias and lymphomas and isolation of a new type-C retrovirus, properties of sarcoma growth factors produced by sarcoma virus transformed cells, and interactions of murine leukemia viruses with hematopoietic stem cells. Mechanisms in chemical carcinogenesis are discussed with respect to activation of carcinogenic polycyclic hydrocarbons by metabolism, involvement of a protein kinase in multistage skin tumor promotion, and the effect of tumor-causing chemicals on the control of mutagenesis and differentiation in mammalian cells. Transformation of cloned mammary epithelial cells following combined treatment with mouse mammary tumor virus and dimethylbenz(a)anthracene, virus-cell interactions during hormonal carcinogenesis, and separate pathways for viral and chemical carcinogenesis in the mouse mammary gland are described. A molecular approach to studies of chemical carcinogen-virus interaction is presented. Other presentations deal with multistage recombinational origin of leukemogenic viruses, radiation-induced leukemogenesis, neoplastic transformation of cultured cells by herpes simplex virus type 2 and carcinogens, modulation of adenovirus transformation and replication, and transformation of murine fibroblasts. (682 Refs)

53. SPONTANEOUS NEOPLASTIC PATHOLOGY IN CONTROL RATS - A REVIEW.

Nunziata A, Storino AA
Centro Ricerca Farmaceutica, Via Tito Speri, 14 Pomezia, Roma, Italy
Vet Hum Toxicol; 24(4):243-247 1982

Data on spontaneous occurrence of neoplasms in strains of rats used in laboratory studies were tabulated from several published sources, and included data on strain, age, diet, length of experiment, number of animals, number of tumor-bearing animals, and the percentages of various types of tumors separated by sex. Both sexes of Wistar rats had the highest spontaneous neoplastic incidence, with values ranging from 56%-96% for males and from 32-90% for females. Sprague-Dawley rats had incidences ranging from 8-50%. Pituitary, mammary gland, lymphoid, skin, adrenal, and gonadal tumors were most frequently observed. Wistar rats had a spontaneous incidence of thyroid tumors varying from 0-32% for males and 0-31% for females, whereas other strains had a remarkably low incidence of these tumors. It is suspected that diet plays a major role in influencing spontaneous carcinogenesis, but little information is available to support this hypothesis. An internationally standardized diet of defined characteristics is recommended, with monitoring of aflatoxin, ocratoxin, polycyclic hydrocarbons, and heavy metal levels within specified limits. (39 Refs)

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Chemical Industry Inst. Toxicology, Research Triangle Park, NC, 27709
Ann NY Acad Sci; 381:43-53 1982

2. PRODUCTION OF BRAIN TUMORS WITH AROMATIC HYDROCARBONS.
Zimmerman HM
Montefiore Hosp. and Medical Center, 111 East 210th St., Bronx, NY, 10467
Ann NY Acad Sci; 381:320-324 1982

3. ORAL CONTRACEPTIVE STEROIDS AND MALIGNANCY.
Grant E
No affiliation given
Clin Oncol; 8(2):97-102 1982

4. METAL CARCINOGENESIS - WHAT IS REAL (MEETING ABSTRACT).
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